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CONTENTS OF PREVIOUS NUMBERS

MARCH, 1922. NUMBER 3

Chronic Nephritis in Childhood. Report of a Case with Review of the Literature. Carl H. Greene, Rochester, Minn.

The Antiscorbutic Property of Fruits. II. An Experimental Study of Apples and Bananas. Maurice H. Givens, H. B. McClugage and E. G. Van Horne, Rochester, N. Y.

Indices of the State of Nutrition in Children. H. Gray, M.D., and G. H. Edmands, Boston.

Studies in Infant Feeding. XVI. A Bacteriologic Study of the Feces and the Food of Normal Babies Receiving Breast Milk. Elsie W. Brown and Alfred W. Bosworth, Boston.

Results Following the Administration of Alkali Phosphates to Spasmophilic, Rachitic and Normal Infants. Joseph K. Calvin, S.B., M.D., and Maxwell P. Borovsky, S.B., M.D., Chicago.

Clinical Department:
A Case of Alkaptonuria in an Infant. J. B. Bilderback, M.D., Portland, Ore.

Progress in Pediatrics:
Review of the Literature on Respiratory Diseases from January, 1920, to June, 1921. Philip Moen Stimson, M.D., New York City (to be continued).

APRIL, 1922. NUMBER 4

Indications for the Removal of the Spleen in Infants and Children. Frederic H. Bartlett, M.D., New York.

The Bacteriology of the Normal Infant's Urine. Henry F. Helmholz, M.D., and Frances Millikin, Rochester, Minn.

The Value of Cutaneous Sensitization Tests Employed in Eczema and Papular Urticaria of Childhood. D. M. Sidlick, M.D., and Frank Croxer Knowles, M.D., Philadelphia.

Studies of Infant Feeding. XVII. A Bacteriochemical Study of the Acid Stools Excreted by Breast-Fed and Bottle-Fed Infants. Alfred W. Bosworth, H. Kenneth Wilder, Marguerite E. Blanchard, Elsie W. Brown and Marion F. McCann, Boston.

Progress in Pediatrics:
Review of the Literature on Respiratory Diseases from January, 1920, to June, 1921 (Concluded). Philip Moen Stimson, M.D., New York City.

MAY, 1922. NUMBER 5

Nephritis in Children. Gladys Boyd, M.D. (Tor.), Toronto.

Eczema in Breast-Fed Infants as a Result of Sensitization to Foods in the Mother's Dietary. W. Ray Shannon, M.S., M.D., St. Paul.

Sitting-Height and Stem-Length in Private Schoolboys. H. Gray, M.D., Boston.

The Presence of Formic Acid in the Urine of Infants and Older Children. Morley D. McNeal, M.D., Rochester, Minn., and Charles J. Eldridge, M.D., Chicago.

The Prophylactic and Therapeutic Value of Pertussis Vaccine. G. R. Davies, M.D., Syracuse, N. Y.

The Chlorin Content of Cows' and Goats' Milk and Formulas Commonly Used in Infant Feeding. Warren R. Sisson, M.D., and W. Denis, Ph.D., Boston.

Clinical Department:
Respiratory Obstruction Resulting in Death. Case Report with Necropsy Findings. James W. Bruce, M.D., and Stuart Graves, M.D., Louisville, Ky.

Progress in Pediatrics:
A Review of the Literature of Syphilis in Infancy and Childhood. Park J. White, M.D., St. Louis.

Book Reviews.

JUNE, 1922. NUMBER 6

The Food Requirements of Children. III. Fat Requirement. L. Emmett Holt, M.D., and Helen L. Fales, New York.

The Frequency of Tuberculosis in Childhood. Franz Hamburger, Styria, Austria.

Idiopathic Aplastic Anemia. Report of Case in a Child Four Years Old; Marked Improvement from Transfusion. Charles Herrman, M.D., New York.

Spasmophilia and the Alkali Reserve of the Blood. Joseph K. Calvin, S.B., M.D., and Maxwell P. Borovsky, S.B., M.D., Chicago.

The Aspiration of Stearate of Zinc in Infancy. A Clinical and Experimental Study. Henry Heiman, M.D., and Paul W. Aschner, M.D., New York.

The Vitamin Requirement of Various Species of Animals: III. The Production and Cure of Xerophthalmia in the Suckling. Victor E. Nelson, Alvin R. Lamb and V. G. Heller, Ames, Iowa.

Active Immunization of Nurses Against Diphtheria in a Children's Hospital. J. V. Cooke, M.D., St. Louis.

Healing of Hypertrophic Pyloric Stenosis After the Fredet-Rammstedt Operation. Martha Wolestein, M.D., New York.

A Peculiar Eruptive Disease Occurring in Infancy. James H. Park, Jr., M.D., and Jeffrey C. Michael, M.D., Houston, Texas.

The Value of the Intracutaneous Tuberculin Test in Extensive Tuberculosis. William H. Happ and Horton R. Casparis, Baltimore.

The Bacteriolysant Therapy of Bacillary Dysentery in Children. Therapeutic Application of Bacteriolysants; D'Herelle's Phenomenon. Wilburt C. Davison, M.D., Baltimore.

Progress in Pediatrics:
A Review of the Literature of Syphilis in Infancy and Childhood. Park J. White, M.D., St. Louis (Concluded from Page 469).

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CONTENTS OF VOLUME 24

JULY, 1922. NUMBER 1 PAGE

BILATERAL HYPOPLASTIC CYSTIC KIDNEYS. REPORT OF A CASE SIMULATING CHRONIC DIFFUSE NEPHRITIS IN A GIRL THREE YEARS OF AGE. CARL H. GREENE, ROCHESTER, MINN. 1

ULTRAVIOLET RADIATION IN RICKETS. EFFECT ON THE CALCIUM AND INORGANIC PHOSPHOROUS CONCENTRATION OF THE SERUM. B. KRAMER, H. CASPARIS AND J. HOWLAND, BALTIMORE 20

THYMUS APOPLEXY. AN UNUSUAL MANIFESTATION OF HEMORRHAGIC DISEASE OF THE NEWLY BORN. H. R. WAHL, M.D., AND DAMON WALTHALL, M.D., ROSEDALE, KAN. 27

THE FOOD REQUIREMENTS OF CHILDREN. IV. CARBOHYDRATE REQUIREMENT. L. EMMETT HOLT, M.D., AND HELEN L. FALES; NEW YORK... 44

FOOD REQUIREMENTS IN NEW-BORN INFANTS. A STUDY OF THE SPONTANEOUS INTAKE. HAROLD K. FABER, SAN FRANCISCO 56

DATA IN THREE THOUSAND SEVEN HUNDRED AND FORTY-TWO PIRQUET TESTS. STAFFORD MCLEAN, M.D., NEW YORK, AND HELMINA JEIDELL, M.D., SALT LAKE CITY 73

THE VITAL CAPACITY OF THE LUNGS OF CHILDREN. A PRELIMINARY REPORT. CHESTER A. STEWART, M.D., PH.D., MINNEAPOLIS, AND O. B. SHEETS, M.D., HOLLYWOOD, CALIF. 83

NEUROPATHIC MANIFESTATIONS IN INFANTS AND CHILDREN AS A RESULT OF ANAPHYLACTIC REACTION TO FOODS CONTAINED IN THEIR DIETARY. W. RAY SHANNON, M.D., ST. PAUL 89

AUGUST, 1922. NUMBER 2

THE BASAL METABOLISM OF PREMATURITY. II. RELATION OF BASAL METABOLISM TO CALORIC INTAKE AND WEIGHT CURVE. FRITZ B. TALBOT, WARREN R. SISSON, MARGARET E. MORIARITY AND ALICE J. DALRYMPLE, BOSTON 95

INFLUENZAL MENINGITIS. T. M. RIVERS, M.D., BALTIMORE 102

STUDIES OF NEPHRITIS IN CHILDREN. I. NEPHROSIS. HERMAN SCHWARZ, M.D., AND JEROME L. KOHN, M.D., NEW YORK 125

ORAL DISORDERS IN PEDIATRICS. SAMUEL A. COHEN, M.D., BOSTON 160

AN EPIDEMIC OF STREPTOCOCCUS HEMOLYTICUS SEPTICEMIA. L. HOWARD SMITH, PORTLAND, ORE. 171

BOOK REVIEW 178

SEPTEMBER, 1922. NUMBER 3

THE HORSE SERUM (FOREIGN PROTEIN) TREATMENT OF PYELITIS AND PYURIA. DAVID MURRAY COWIE, M.D., ANN ARBOR, MICH. 179

DYSKERATOSIS DIFFUSA CONGENITA. CORNELIA DE LANGE, M.D., AND J. C. SCHIPPERS, M.D., AMSTERDAM. 186

THE THYMIC SHADOW IN INFANTS. I. EDWARD LISS, M.D., SCARDALE, N. Y. 192

THE INORGANIC PHOSPHATE CONTENT OF BREAST MILK OF MOTHERS WITH NORMAL AND WITH RACHITIC INFANTS. LUDO VON MEYSENBUG, M.D., NEW ORLEANS 200

INDICATIONS FOR TONSILLECTOMY IN INFANCY AND CHILDHOOD. IS THE MODERN TENDENCY TOWARD UNIVERSAL TONSILLECTOMY JUSTIFIED? HENRY HEIMAN, M.D., NEW YORK 204

APPLIED DIETETICS IN OUTPATIENT DEPARTMENTS. MAYNARD LADD, M.D., BOSTON 211

ACUTE INFECTIONS OF THE URINARY TRACT IN INFANTS AND CHILDREN SUBSIDING WITHOUT THE APPEARANCE OF PUS IN THE URINE. WALTER R. RAMSEY, M.D., ST. PAUL 218

A CRITICAL STUDY OF SIXTY-ONE CASES OF ASTHMA AND ECZEMA IN INFANCY AND CHILDHOOD CONTROLLED BY CUTANEOUS PROTEIN SENSITIZATION TESTS. HAROLD HERMAN, M.D., NEW YORK 221

CLINICAL DEPARTMENT:

A CASE OF MYELOID CHLOROMA. O. W. ROWE, M.D., AND F. J. HIRSCHBOECK, M.D., DULUTH, MINN. 239

PROGRESS IN PEDIATRICS:

THE ALLERGIC OR HYPERSENSITIVE CONDITION: A REVIEW OF TWO YEARS' PROGRESS. ALLAN R. CUNNINGHAM, M.D., BOSTON 247

418858

OCTOBER, 1922. NUMBER 4 PAGE

THE AMOUNT OF BLOOD TO BE TRANSFUSED IN ANEMIA OF CHILDREN (BLOOD DOSAGE). TJ. HALBERTSMA, HAARLEM, HOLLAND..... 269
THE DIAGNOSIS AND TREATMENT OF INTRACRANIAL HEMORRHAGE IN THE NEW-BORN. A REPORT OF FOURTEEN TREATED CASES. DONALD MUNRO, M.D., AND RICHARD S. EUSTIS, M.D., BOSTON..... 273
CONGENITAL DEFICIENCY OF THE DIAPHRAGM. JOHN STEPHENS LATTA, OMAHA 297
EXPERIMENTAL PYLORIC STENOSIS. I. HARRISON TUMPEER, M.D., AND M. A. BERNSTEIN, M.D., CHICAGO..... 306
THE FOOD REQUIREMENTS OF CHILDREN. V. PERCENTAGE DISTRIBUTION OF CALORIES. L. EMMETT HOLT, M.D., AND HELEN L. FALES, NEW YORK. 311
THE USE OF RADIANT HEAT—LIGHT—IN THE TREATMENT OF OTITIS MEDIA. H. J. GERSTENBERGER, M.D., AND C. T. J. DODGE, M.D., CLEVELAND 320
INFANTILE RICKETS: THE SIGNIFICANCE OF CLINICAL, RADIOGRAPHIC AND CHEMICAL EXAMINATIONS IN ITS DIAGNOSIS AND INCIDENCE. ALFRED F. HESS AND LESTER J. UNGER, NEW YORK..... 327
THE FAILURE OF YEAST THERAPY IN THE FEEDING OF INFANTS. WILBURT C. DAVISON, M.D., BALTIMORE..... 339
RABBIT HAIR ASTHMA IN CHILDREN. BRET RATNER, M.D., NEW YORK.. 346
CLINICAL DEPARTMENT:
DIAPHRAGMATIC HERNIA IN A NEW-BORN. REPORT OF A CASE. CLARA M. DAVIS, M.D., CLEVELAND..... 356

NOVEMBER, 1922. NUMBER 5

D'ESPINE'S AND ALLIED SIGNS IN CHILDHOOD. JOHN LOVETT MORSE, A.M., M.D., BOSTON..... 361
A CLINICAL AND CHEMICAL STUDY OF BUTTER SOUP FEEDING IN INFANTS. ALAN BROWN, M.B., A. M. COURTNEY, B.A., AND I. F. MACLACHLAN, B.A., TORONTO 368
THE CALCIUM AND PHOSPHORUS CONCENTRATION IN THE SERUM OF INFANTS WITH MILD RICKETS OR A CONDITION SIMULATING MILD RICKETS. FREDERICK F. TISDALL, M.D. (TOR.), TORONTO..... 382
THE INCIDENCE OF MENINGITIS IN EARLY INFANCY, WITH A DESCRIPTION OF TWO CASES DUE TO UNUSUAL ORGANISMS. J. V. COOKE, M.D., AND HOWARD H. BELL, M.D., ST. LOUIS..... 387
A STUDY OF THE SHADOWS IN THE THORAX OF THE NEWLY-BORN. L. R. DEBUYS, M.D., AND ERNEST C. SAMUEL, M.D., NEW ORLEANS..... 397
GASTRIC MOTILITY AFTER PYLORIC OBSTRUCTION IN INFANCY. BORDEN S. VEEDER, MALVERN B. CLOPTON AND R. WALTER MILLS, ST. LOUIS 404
THE RATE OF SECRETION OF BREAST MILK. CHARLES HENDEE SMITH, M.D., AND KATHERINE K. MERRITT, M.D., NEW YORK..... 413
INTRAVENTRICULAR AND SUBDURAL SERUM TREATMENT OF MENINGOCOCCUS MENINGITIS IN INFANCY. WILLIAM W. HOWELL, M.D., AND SAMUEL ADAMS COHEN, M.D., BOSTON..... 427
THE INCIDENCE OF THYMIC ENLARGEMENT WITHOUT SYMPTOMS IN INFANTS AND CHILDREN. ROY M. GREENTHAL, M.D., MILWAUKEE.. 433
CLASSIFICATION AND MANAGEMENT OF ASTHMA IN CHILDHOOD. THE IMPORTANCE OF RABBIT HAIR AS A CAUSE IN NEW YORK CITY. NILS P. LARSEN, M.D., AND SAMUEL D. BELL, M.D., NEW YORK CITY..... 441
BOOK REVIEW 450

DECEMBER, 1922. NUMBER 6

THE VITAL CAPACITY OF THE LUNGS OF CHILDREN IN HEALTH AND DISEASE. CHESTER A. STEWART, M.D., PH.D., MINNEAPOLIS..... 451
DEHYDRATION IN NEW-BORNS, I. HARRY BAKWIN, M.D., WITH THE TECHNICAL ASSISTANCE OF CATHERINE GOSS, A.B., NEW YORK..... 497
DEHYDRATION FEVER IN NEW-BORNS, II. HARRY BAKWIN, M.D., WITH THE TECHNICAL ASSISTANCE OF CATHERINE GOSS, A.B., NEW YORK..... 508
THE TREATMENT OF ACCESSORY NASAL SINUS DISEASE IN CHILDREN. H. B. LEMERE, M.D., OMAHA..... 520
A NEW ERUPTIVE FEVER ASSOCIATED WITH STOMATITIS AND OPHTHALMIA. REPORT OF TWO CASES IN CHILDREN. A. M. STEVENS, M.D., AND F. C. JOHNSON, M.D., NEW YORK..... 526
CONGENITAL DUODENAL OBSTRUCTION: MALROTATION OF THE INTESTINE. REPORT OF CASE. B. S. DENZER, M.D., NEW YORK..... 534
INDEX 541

American Journal of Diseases of Children

VOL. 24 JULY, 1922 NO. 1

BILATERAL HYPOPLASTIC CYSTIC KIDNEYS

REPORT OF A CASE SIMULATING CHRONIC DIFFUSE NEPHRITIS IN A GIRL THREE YEARS OF AGE *

CARL H. GREENE

ROCHESTER, MINN.

Functional insufficiency of the kidney in early infancy produces characteristic clinical findings. These are best seen in cases of congenital chronic nephritis.[1] Children so affected show great developmental disturbances dating from early life, if not from birth. Associated with the developmental disturbance are stunting and backwardness in growth, difficulty in feeding, anemia and rachitis. More direct evidence of renal insufficiency is given by the excretion of a large volume of dilute urine with a low specific gravity. This urine contains a slight amount of albumin, and casts are present in small numbers. In those cases in which it has been determined, the phenolsulphonepthalein excretion is low. Death usually results from uremia. The pathologic picture in these cases is similar to, if not identical with, that seen in the chronic diffuse nephritis of adults.

The clinical findings in such cases, however, are determined by the functional rather than by the morphologic changes in the kidneys. Any renal lesion that will cause the same type of renal insufficiency will produce the same clinical changes. I wish to report a case in which the clinical symptomatology was identical with that described above, but in which the functional changes were produced by an entirely different renal lesion.

REPORT OF CASE

M. V. W. (Harriet Lane Dispensary, No. 20620), aged 3½ years, of American parentage.

Family History.—Unimportant. Third pregnancy. The second child was stillborn at full term. No history of nephritis in any of the immediate relatives.

Past History.—Spontaneous delivery at term. Birth weight, 5 pounds. The child was breast fed for only a short time and then was placed on whole cow's milk to the age of 8 months. The whole milk was then replaced by condensed milk with the addition later of a little rice and potato. The first teeth appeared

* Received for publication, April 14, 1922.

* From the Department of Pediatrics and the Pathologic Laboratory, Johns Hopkins University, and the Harriet Lane Home of the Johns Hopkins Hospital.

1. Greene, C. H.: Chronic Diffuse Nephritis in Childhood. Report of a Case with a Review of the Literature, Am. J. Dis. Child. **23**:183 (March) 1922.

when 1 year old. She sat alone at this time though she never walked. At the age of 8 months she is said to have had several convulsions in immediate succession, followed by stupor for the next day or two and then by pneumonia. When about 2 years old there was a similar illness accompanied by five convulsions in one day. No convulsions have followed this second attack though there was a history of irregular "spells of fever."

Examination at the first visit to the dispensary showed an underdeveloped child with a marked degree of rachitis. The urine contained a trace of albumin but no casts. The patient was treated in the dispensary for five months, during which time regulation of her diet was attempted and cod liver oil, phosphorus and bitter wine of iron were given. The weight increased, from 21 to 22 pounds, but feeding was difficult and she never ate well. She was admitted to the Harriet Lane Home August 1, with a temperature of 103 F. after having been feverish and irritable for about a week.

Physical Examination.—The patient was a markedly undernourished and underdeveloped child. Though 3½ years old the weight was only 22 pounds (average weight for age 33.5 pounds). Anemia was marked and the skin presented a uniform ivory-like pallor. The child was rachitic with extreme deformity of the head, chest and extremities. Muscular development was poor although she was able to sit up unsupported. No effort was made to stand or walk and the tibial bowing would have rendered the feat difficult. She talked with a fair degree of distinctness and there was no apparent mental retardation.

Head: Typically rachitic in shape, large and square with pronounced frontal and parietal bosses. The anterior fontanel was open admitting one finger tip. The eyes and ears were normal. The throat showed slight injection of the pharynx and hypertrophy of the tonsils. The lips and mucous membranes were anemic.

Chest: Markedly rachitic in type with great flattening of the sides and a nearly rectangular cross section. Harrison's groove was prominent and was further accentuated by the flaring of the lower ribs. A distinct rosary was present. Respirations were quiet; abdominal in type.

Lungs: Clear on percussion and auscultation.

Heart: The relative cardiac dullness measured 1 by 6.5 cm. at the fifth interspace with the point of maximum impulse 6 cm. from the midsternal line. The heart sounds were clear and the aortic second sound was not accentuated. The pulse was regular in rate and rhythm and of good quality.

Abdomen: Large and distended. The muscle tone was poor. No fluid could be made out. The liver was enlarged, extending 4 cm. below the costal margin. The edge was smooth and sharp. The spleen was greatly enlarged, measuring 6 by 10 cm. and extending from the twelfth rib behind nearly to the iliac crest and a third of the way to the umbilicus anteriorly. The kidneys were not palpable.

Extremities: Marked distortion of all the long bones was present. The humeri appeared relatively short owing to bowing. The radius was nearly 1 cm. longer than the ulna, leaving the hand in a position of extreme adduction. The femora also showed bowing. The lower third of the tibia was bent posteriorly through an angle of nearly 90 degrees leaving the long axis of the foot in a plane parallel to the axis of the leg. Muscular weakness was marked.

Tendon reflexes: Present and equal on both sides though they were very feeble.

Laboratory Reports.—Blood examination: Leukocytes, 13,350; erythrocytes, 2,460,000; hemoglobin (Sahli), 43 per cent. Differential count: Polymorphonuclear neutrophils, 35 per cent.; polymorphonuclear eosinophils, 6 per cent.; polymorphonuclear basophils, none; lymphocytes, 33 per cent.; pathologic lymphocytes, 9 per cent.; large mononuclears, 3 per cent.; transitionals, 6 per cent.; myelocytes, 1 per cent.; myeloblasts, 2 per cent.; unclassified, 5 per cent. The red cells were pale with some poikilocytosis and rather marked anisocytosis. The platelets were diminished in number. The blood picture was that of a severe secondary anemia with a moderate degree of bone marrow stimulation.

Fig. 1.—Photograph of the patient. The costal margins and the edge of the liver and spleen are outlined.

Fig. 2.—Roentgenogram of the leg showing the bowing of the tibia and the rachitic changes at the ankle and knee.

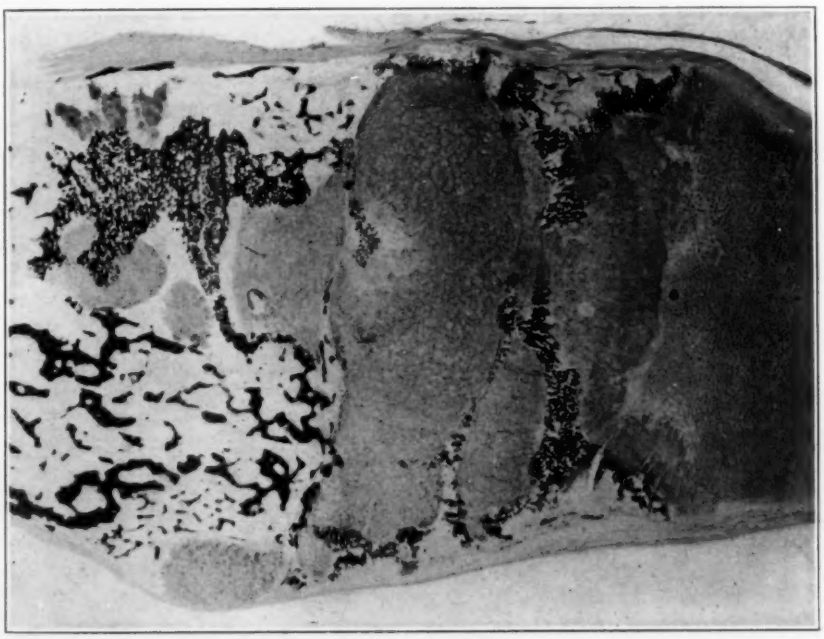

Fig. 3.—Section through the costochondral junction showing the extensive rachitic changes. Three distinct lines of healing. Stained with silver to show the calcium phosphate deposits.

Urine: Pale yellow, faintly acid. Specific gravity, 1.009. Albumin (Esbach), 1.5 gm. per liter. A trace of acetone was present. No sugar, bile or blood. Microscopic examination showed many epithelial cells, a few pus cells but no casts.

Phenolsulphonephthalein excretion in two hours was 7 per cent.

Total urine: Twenty-four hour specimen of urine showed some polyuria and a distinct tendency toward fixation of the specific gravity and nitrogen concentration. Day urine, 9 a. m. to 9 p. m.: 400 c.c., specific gravity, 1.009; nitrogen, 0.22 per cent. Night urine, 9 p. m. to 9 a. m.: 260 c.c.; specific gravity, 1.011; nitrogen, 0.22 per cent. Total urine in twenty-four hours: 660 c.c.; specific gravity, 1.010; nitrogen, 0.22 per cent.

Wassermann and tuberculin reactions were negative.

Course in Hospital.—The temperature returned to normal soon after admission but food was refused or only taken poorly. In addition to the polyuria, polydipsia and pollakiuria were marked. A repetition of the phenolsulphonephthalein test on a catheterized specimen gave a 4 per cent. return.

There was no marked change in the general condition until August 6, when the child became very much weaker, developed hyperpnea and became stuporous. Respirations were slow, labored and stertorous. The pulse was weak and feeble with a marked pulsus alternans. The maximum systolic blood pressure varied between 100 and 108 with nearly 20 mm. difference in the systolic pressure of alternate beats. The diastolic blood pressure was between 65 and 70. The carbon dioxid capacity of the blood at this time was 18 volumes per cent. and the nonprotein nitrogen was 48 mg. per 100 c.c. Examination of the eye grounds revealed slight diffuse congestion, but no suggestion of albuminuric retinitis. Sodium bicarbonate was given by mouth in large doses with gradual improvement. The following day the carbon dioxid capacity of the blood had increased to 26 volumes per cent. Two days later the hyperpnea ceased though the urine continued to show large quantities of acetone and diacetic acid. Five days later (August 13) the patient had apparently recovered and was in fairly good condition. She was brighter and more alert and able to take her feedings well.

There was very little change in the general blood picture. Leukocytes, 17,500; erythrocytes, 2,590,000; hemoglobin (Sahli), 41 per cent.

Urine: A clear, lemon yellow, acid specimen. Specific gravity, 1.012. Albumin (Esbach) 1.75 gm. per liter. No acetone or diacetic acid present.

Phenolsulphonephthalein excretion in two hours was 6 per cent.

Carbon dioxid capacity of the blood was 35 volumes per cent. Blood pressure: systolic, 96; diastolic, 60; with no alterations of the pulse.

At this time a cystoscopic examination was made. Abdominal palpation under anesthesia was apparently negative, as neither kidneys nor ureters could be palpated, though the liver, spleen and pancreas were easily felt. Cystoscopic examination showed a normal bladder. Urine cultures were negative.

Owing to the poor condition of the patient (the weight had fallen to 18 pounds) and the increasing anemia, transfusion was determined on. August 16, the child was given 175 c.c. of citrated whole blood from the father. There was no reaction following the transfusion other than a slight rise in temperature. Improvement in the appetite and general condition was marked. Four days after transfusion the carbon dioxid capacity of the blood was 41 volumes per cent.

Blood examination: Leukocytes, 9,000; erythrocytes, 3,560,000; hemoglobin (Sahli), 60 per cent. Differential count: Polymorphonuclear neutrophils, 26 per cent.; polymorphonuclear eosinophils, 4 per cent.; polymorphonuclear basophils, 5 per cent.; lymphocytes, 37 per cent.; pathologic lymphocytes, 8 per cent.; large mononuclears, 1 per cent.; transitionals, 5 per cent.; myelocytes, none; myeloblasts, 1 per cent.; unclassified, 13 per cent. The red cells were essentially normal. There were many poorly stained and fragile forms of leukocytes difficult of interpretation, but they were probably mostly lymphocytes.

Urine: Slightly cloudy, pale yellow specimen, acid. Specific gravity, 1.012. Albumin (Esbach), 0.75 gm. per liter. No acetone or diacetic acid. Epithelial and a few pus cells were present but no casts.

Phenolsulphonephthalein: The two hour excretion was 8 per cent.

The child continued to improve rapidly. She ate fairly well, but continued to be particular as to her diet, refusing eggs, though taking bread and milk, and gaining in weight. She was bright and alert. The pollakiuria became less marked but total samples were not saved so that we are unable to state whether this change was due to a lessening of the degree of polyuria or rather to lessened bladder irritability. Blood examination, September 1: Leukocytes, 14,000; erythrocytes, 2,960,000; hemoglobin (Sahli), 70 per cent. There was no change in the differential count. The red cells were dark with some diffuse basophilia. Platelets were still diminished. Four normoblasts were seen.

Fig. 4.—The two kidneys compared with a normal kidney from a child of the same age.

Urine: Pale yellow specimen, acid; specific gravity, 1.013. Albumin (Esbach), 0.75 gm. per liter. No acetone or diacetic acid. No casts or pus cells.

Phenolsulphonephthalein: The two hour excretion was 10 per cent.

The patient's condition at this time was sufficiently satisfactory to warrant her discharge from the hospital. Weight, 20 pounds 6 ounces.

She proved to be difficult to manage at home. Her appetite became progressively poor and capricious so that finally she refused all food other than milk, rice and potatoes. She was given reduced iron, but the hemoglobin fell rapidly. She developed a cough and began to lose weight and was readmitted to the Harriet Lane Home, September 26.

Examination at this time showed evidences of a severe anemia and recent loss of weight. There was a slight rhinopharyngitis. The patient's condition

otherwise was the same as on her first admission to the hospital. The measurements of the liver and spleen were identical with the earlier ones. The systolic blood pressure was 102, the diastolic, 68.

Blood examination, September 26: Leukocytes, 13,900; erythrocytes, 2,496,000; hemoglobin (Sahli), 28 per cent.

Urine: Pale yellow specimen, acid; specific gravity, 1.011. Albumin positive. No acetone or diacetic acid. A few epithelial and white blood cells were present but no casts or red blood cells.

Phenolsulphonephthalein. The two hour excretion was 7 per cent.

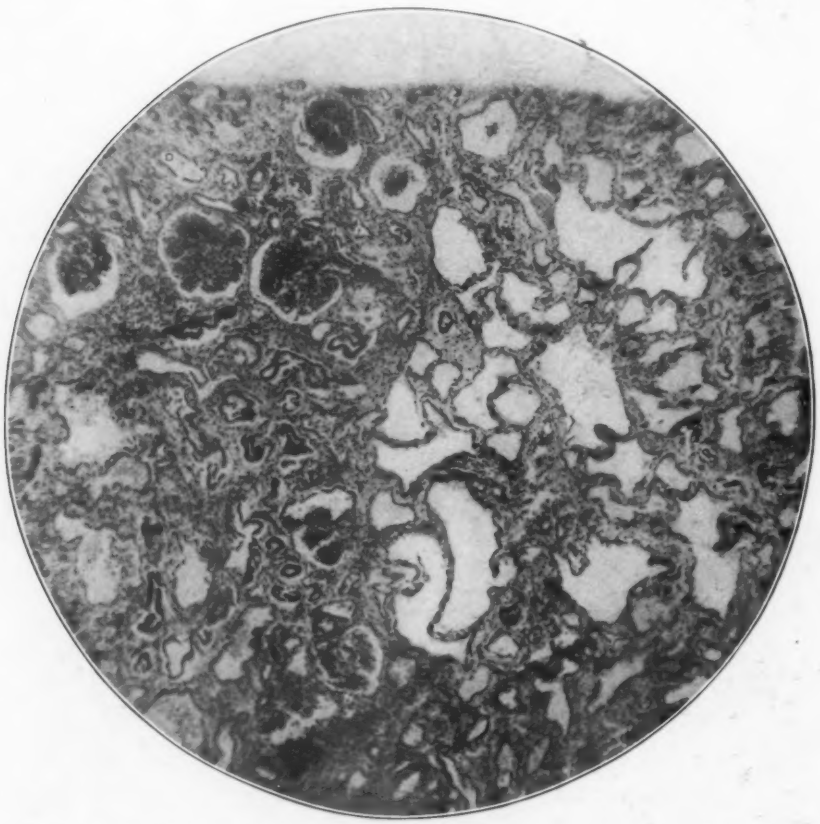

Fig. 5.—Cortex of the kidney showing the large peripherally situated glomeruli and the enormously dilated tubules.

The patient continued to present a difficult feeding problem during the remainder of her hospital course. She persistently refused all food but milk, rice and potatoes though she could be forced to eat small amounts of egg, scraped beef and vegetables.

An Ewald breakfast October 12 revealed the presence of an hypochlorhydria. Removed at one hour it showed free hydrochloric acid, none; combined acid, 24; hydrochloric acid deficit, 40.

Dilute hydrochloric acid was then given in the hope that the appetite might be improved, but unavailingly. The child continued rapidly to lose weight.

Slight hyperpnea was observed October 18 and the carbon dioxid capacity of the blood was found to be 19 volumes per cent. The hydrochloric acid was then discontinued and sodium bicarbonate substituted.

October 24, the child's condition underwent a distinct change for the worse, associated with a progressively rising temperature and a rapid loss of weight. Vomiting made it necessary to stop all feedings and administer fluids by means

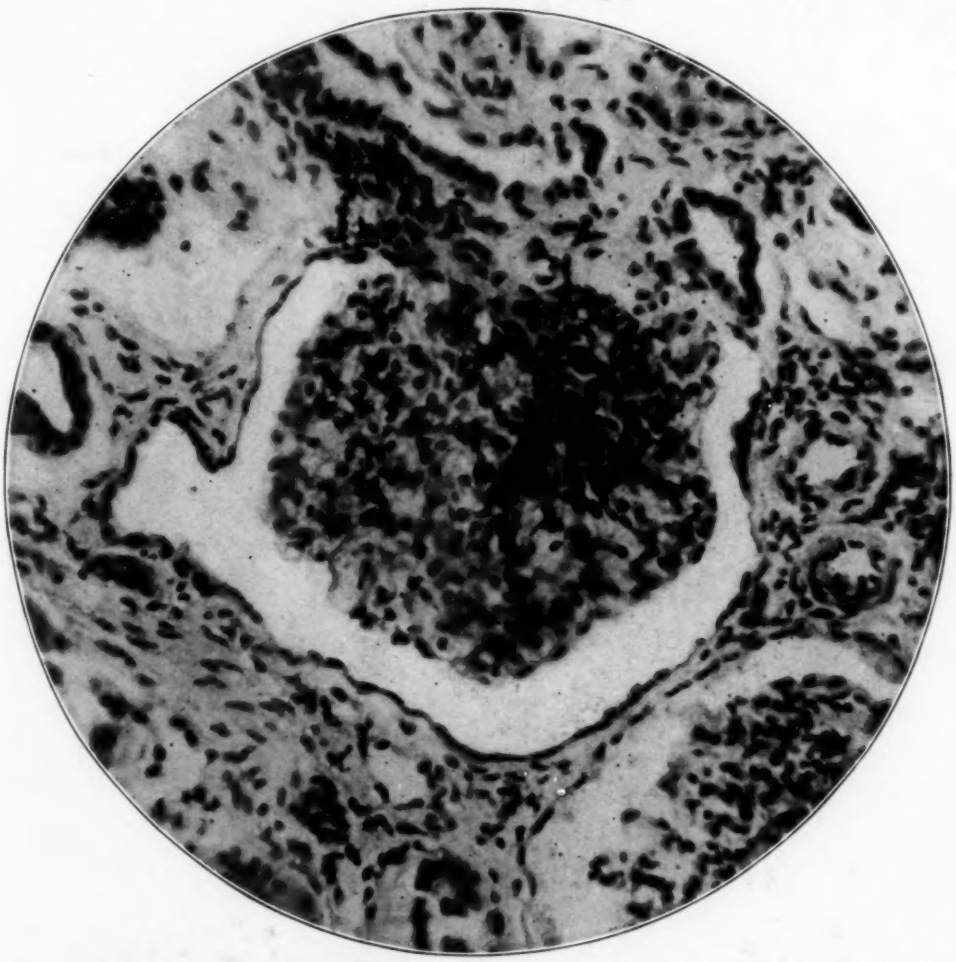

Fig. 6.—Glomerulus showing the dilatation of Bowman's capsule and the round cell infiltration through the section.

of the rectal drip method. Anuria developed October 27. The temperature remained in the neighborhood of 103 F. and death ensued on the following day.

Macroscopic Findings (No. 6038).[2]—Body: The body was that of a small child greatly undersized for her age. The skin showed an extreme pallor and there were marked rachitic deformities present, accompanied by muscular

2. I am indebted to Dr. J. Paul of the Department of Pathology for permission to report the necropsy findings.

atrophy. The long bones of both arms and legs showed epiphyseal enlargements and symmetrical bowing of the shafts, especially the tibias. Saber-shin and toe-drop deformities were present. The axillary and cervical lymph glands were easily palpable.

On opening the peritoneal cavity the abdominal viscera appeared to be unusually pale. The serous surfaces were smooth and the cavity contained no fluid. The viscera were normally disposed but the liver, slightly enlarged,

Fig. 7.—Dilated and cystlike tubule showing the flattened epithelium, the communication between the different cysts, and the cellular débris filling the tubules.

projected 1.5 cm. below the costal margin and the inferior end of an enlarged spleen was visible. Prominent and numerous lymph glands appeared in the mesentery.

The thoracic cavity was narrow and compressed and the enlargements of the costochondral junctions stood out on its external surface and projected into the pleural cavities as nodules on the anterior thoracic wall. The heart

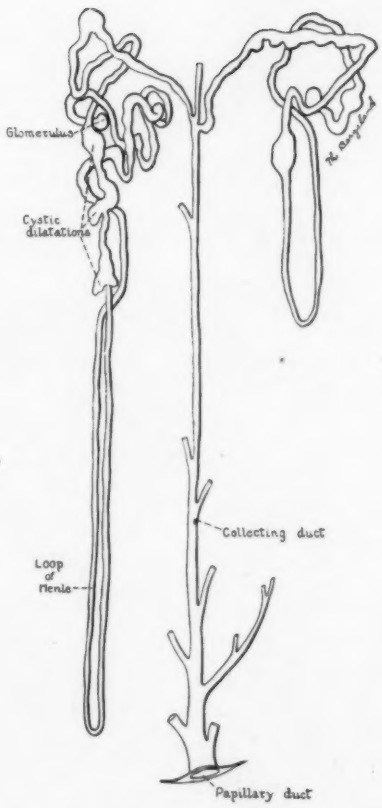

Fig. 8 Fig. 9

Fig. 8.—Semidiagrammatic sketch to show the general relationship of the renal tubules and the cystic dilatations. Made from a dissection of the tubules by Dr. H. F. Traut.

Fig. 9.—Wax reconstruction of a dilated tubule to show the character of the cystic dilatations. The glomerulus, the proximal convoluted tubule, the loop of Henle and the beginning of the distal convoluted tubule are shown.

occupied the major portion of the lower thorax, its apex lying close to the left thoracic wall while the lower lobe of the left lung was practically entirely anterior to it.

Heart: No hypertrophy of the heart was present; it was small, weighing only 50 gm. Both epicardium and endocardium were smooth. The valves were delicate and apparently competent. The myocardium appeared to be normal.

Lungs: Both lungs were small and almost white in color, their consistency being everywhere soft and cushiony. The pleural surfaces showed an unusual degree of wrinkling. They were pale and somewhat opaque in appearance. On section the cut surface showed slightly atelectatic lung tissue.

Spleen: The spleen was of unusual appearance. It was large, weighing 100 gm. and measuring 9.5 by 4.5 by 2.5 cm. It was dark purple in color and very firm in consistency. It was tense and smooth. On section the splenic pulp was dark red and firm. Many prominent, but small, greyish malpighian bodies were visible.

Mesenteric lymph glands: These glands, averaging 0.5 cm. in length, appeared in great numbers throughout the proximal portions of the mesentery.

Liver: The liver was large, weighing 500 gm. and measuring 13.5 by 7.5 by 7 cm. Its color was pale brown, in keeping with the pallor of the other organs. It was somewhat mottled and many small fatty areas were present. These were light in color and diffuse in distribution, appearing both on the surface and on section.

Suprarenals: These organs showed no gross abnormalities.

Kidneys: The picture presented by the kidneys was most unusual. Both organs were atrophic, the right more so than the left. The left kidney weighed only 10 gm. and its dimensions were 5 by 3 by 1.5 cm. It was pale grayish red. The surface was quite smooth, the capsule stripped with ease and practically no signs of fetal lobulations were present. On section, the renal pelvis appeared relatively large, considering the small size of the organ. Distortion of the normal kidney architecture was present, and the cortex was very thin and ill defined, measuring about 2 or 3 mm. in width. In its place and in the columns of Bertini and in the distal portions of the medulla the tissue appeared as a fine, loose meshwork, composed of irregularly dilated tubules or innumerable small irregular cysts. The cortical striations were masked by this picture. Throughout the medulla an increase in fibrous tissue was present.

The right kidney was smaller, weighing only 7 gm., and measuring 4 by 2.5 by 1.5 cm. It was similar in appearance to the left. The cortex was again ill defined and almost microscopic.

Both ureters showed some dilatation, the one on the left being slightly larger than the right. No demonstrable ureteral strictures were present.

Bladder: Contained a few cubic centimeters of very cloudy urine. The mucous surface of the bladder was normal but very pale. Over the trigone there were numerous submucous hemorrhages. Hemolytic streptococci, staphylococci and colon bacilli were grown from a urine culture taken at the time of necropsy.

Intestines: Peyer's patches were prominent, especially in the region of the ileocecal valve.

Bones: Great enlargement, as described above, of the costochondral junctions was present. This was especially noticeable from the third to the eighth rib. On section the line of demarcation between cartilage and bone was thick and irregular.

Bone marrow: The marrow from the right femur was unusually hyperplastic. It had the appearance of dark red jelly.

Brain: The brain did not show any gross abnormalities.

Microscopic Findings.—Heart: Sections show normal heart musculature.

Lungs: A considerable degree of atelectasis was present with compression and thickening of the alveolar walls. There was also an excess of peribronchial

fibrosis. A heavy, thick, subpleural layer of fibrous tissue was present and the pleura was elevated into folds which lay lengthwise along the lung surface, compressing the tissue beneath them. There had been metaplasis of the lining cells of the pleura, and instead of the usual flattened serosal cells, the pleura was composed of high columnar cells with distally placed nuclei.

Spleen: There was a noticeable decrease in fibrous trabeculae and a great predominance of endothelial cellular elements present in the splenic pulp. The malpighian corpuscles were prominent, numerous, and showed pale centers filled with large vesicular cells, but with a peripheral ring of dark, small round cells. Throughout the splenic pulp a great number of red blood corpuscles were seen and normoblasts were undoubtedly present.

Liver: The section presented a uniform appearance, but the portal spaces were abnormally distinct, showing an increase in fibrosis and the presence of small round cells and fibroblasts in close association with the bile ducts, a peribiliary reaction. Surrounding these portal spaces there was pronounced vacuolization of the liver cells and peripheral degeneration of the lobules. Signs of a hematogenous function were present, for many of the sinusoids distributed evenly throughout the section contained a few small cells with dark, pyknotic nuclei resembling groups of normoblasts seen in the liver of newly born or premature children.

Suprarenals: Sections of the suprarenals did not show any abnormality.

Kidneys: The microscopic picture will be discussed later.

Bladder: Two sections through the bladder wall, one taken from the region of the trigone and one from the fundus, appeared normal and showed little or no histologic evidence of cystitis.

Costochondral junctions:[3] The rachitic deformities were extreme. The changes in the bones as revealed by both the roentgen-ray and histological examination were most extensive. They differed, moreover, from the changes ordinarily found in rachitis. The proliferative cartilage was most irregular and the calcification was defective. In the deep metaphysis were large islands of cartilage bordered on one or more sides by dense calcium deposits. These islands of cartilage gave the metaphysis, as seen in the roentgenogram, a honeycomb appearance. The trabeculae were thin and the osteoid borders, comparatively speaking, narrow. Surrounding the trabeculae and islands of cartilage and lying between them was loose fibrous tissue. Obviously, for a long time the pathologic condition in the bones had been in a state of flux between healing and relapse.

Bone marrow: A smear taken at the time of necropsy and stained with Wright's stain showed many well-formed red blood cells which varied considerably in size. The number of nucleated forms appeared to be normal; normoblasts markedly predominating. There was no basophilia. The number of white blood cells present was normal. Some myelocytes and an occasional myeloblast were present. Many undifferentiated mononuclear cells with finely reticulated, purplish staining, nuclei were seen. These were the normal, undifferentiated bone marrow cells.

Sections stained with both hemotoxylin and eosin and Wright's stain showed a very hyperplastic marrow. The predominating cells showed large vesicular nuclei, and could not be classified other than as undifferentiated bone marrow cells. Great numbers of early cells of the granular series were present and they predominated over the early red cells. Normoblasts were frequent, but only an occasional megaloblast was seen. Great numbers of large megakaryocytes were seen scattered through the marrow.

DISCUSSION OF CLINICAL FINDINGS

Clinically, the findings in this case were those of a long standing renal insufficiency and were identical with those seen in the cases of

3. I am indebted to Dr. E. A. Park for the discussion of the changes in the bones.

typical chronic interstitial nephritis. In this case the family history was negative. The condition was present from birth but symptoms of renal disturbance first appeared at the age of 8 months. At this time the child had convulsions that probably marked the first of a series of uremic attacks.

Following the convulsions, the patient was put on a faulty diet and evidences of rachitis followed. The character of the diet was due, in part, to the ignorance of the parents, but in even greater measure it was due to the idiosyncrasies of the patient. Difficulty in feeding was always present and during her stay in the hospital the child would eat only milk, rice and potato unless forced to take other things. Similar cases have been reported by Oppenheim [4] and Paterson [5] among others. It is not surprising that an extreme degree of rachitis should develop on such a diet.[6] It must be recognized, however, that other factors [7] may have entered into the development of the rachitis in this child.[8] A marked degree of renal insufficiency was also present.

Blood smears taken in this case showed a pronounced secondary anemia. Similar blood changes are found in many cases of rachitis but the type of anemia found in infants is not specific in character [9] and the anemia in this child may have been due, in part, to the renal insufficiency as well as to the rachitis. The remarkable clinical improvement following a single transfusion is of interest. This is especially so since there apparently was no great stimulation of the hemopoietic system. The increase in the erythrocyte count lasted for about a month which corresponds well with the average life of the

4. Oppenheim, A.: Ueber Schrumpfniere im Kindesalter, Inaug. Dissert. Halle, 1891.

5. Paterson, D. H.: Three Cases of Renal Dwarfism Associated with Curious Bony Changes, Proc. Roy. Soc. Med. **13**: Sec. Dis. Child., 107, 1920.

6. The recent work of McCollum, Simmonds, Shipley and Park [7] has indicated that rachitis may be caused by a disturbance in the balance of inorganic salts in the diet when combined with an insufficiency of an organic factor. Disturbance of the calcium-phosphate ratio was more effective in producing rachitic changes than was the absolute amount of these salts present in the diet. Phosphate retention is known to be an accompaniment of nephritic acidosis. It would seem, therefore, that if renal insufficiency were to disturb the calcium-phosphate balance in the blood of a growing child, rachitis might result. Unfortunately, accurate blood studies were not possible in the present instance, and we are unable to present, at the present time, the experimental data requisite to prove this hypothesis. The problem of "renal rickets" has recently been discussed in detail by Shipley, Park, McCollum and Simmonds.[8]

7. McCollum, E. V.; Simmonds, N.; Shipley, P. G., and Park, E. A.: Studies in Experimental Rickets. VIII. The Production of Rickets by Diets Low in Phosphorus and Fat-Soluble A, J. Biol. Chem. **47**:507, 1921.

8. Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmonds, W.: Is There More Than One Kind of Rickets? Am. J. Dis. Child. **22**:91 (July) 1922.

9. Evans, F. A., and Happ, W. M.: Secondary Anemia of Infants. A Study of the So-Called Infantile Splenic Anemia or Anemia Infantum Pseudoleukemica, Johns Hopkins Hosp. Bull. **33**:1, 1922.

transfused blood corpuscle.[10] During this period there was a great improvement in the general condition of the patient and even a slight increase in the phenolsulphonephthalein output, indicating that the kidneys were functionally benefited by the general improvement.

The functional efficiency of the kidneys in this child was low. Increased frequency of urination had been noticed at home. In the hospital a moderate increase in the fluid intake and output was noted. The specific gravity of the urine was low, the limits of variation being from 1.005 to 1.012. A fixation test was not done, but on comparing the total day and night urines there was a definite suggestion of a fixation of the specific gravity and an inability to concentrate the nitrogenous excreta. As in the case of Paterson the phenolsulphonephthalein excretion was extremely low.

Albumin was present in the urine throughout the whole period of the disease. The amount was increased during the uremic attacks, but was never large. No Bence-Jones or protein body other than serum protein was demonstrable in the urine. Casts were absent even during the terminal stages of the disease.

The blood chemistry has not previously been reported on in this type of case and it is to be regretted that complete blood analysis was not possible. The nonprotein nitrogen was 48 mg. per 100 c.c., a value which may be compared with the figures of Schlutz and Pettibone[11] of from 23 to 40 mg. in the blood of new born infants, of Tileston and Comfort[12] of from 20 to 34 mg., of Leopold and Bernhard[13] of from 19 to 40 mg. in the blood of normal children, and of Leopold and Bernhard[13] of from 34 to 52 mg. in miscellaneous cases of chronic nephritis in childhood. It is apparent that there was a definite nitrogenous retention in the blood even though the type of this retention could not be determined.

The systolic blood pressure was 108 and the diastolic 70. While this may indicate a slight hypertension for a child aged 3½ years, it is not marked. There were no evidences of cardiovascular changes.

Death was due to uremia, though starvation acidosis undoubtedly was a contributing factor.

10. Ashby, W.: Determination of Length of Life of Transfused Blood Corpuscles in Man, J. Exper. Med. **29**:267, 1919.

11. Schlutz, F. W., and Pettibone, C. J. V.: Quantitative Determinations of Nonprotein Nitrogen in the Blood of the New-Born, Am. J. Dis. Child. **10**: 206 (Sept.) 1915.

12. Tileston, W., and Comfort, C. W.: The Total Nonprotein Nitrogen and Urea of the Blood and the Phenolsulphonephthalein Excretion in Children, Am. J. Dis. Child. **10**:278 (Sept.) 1915.

13. Leopold, J. S., and Bernhard, L.: The Nonprotein Nitrogenous Constituents of the Blood and the Phenolsulphonephthalein Test in Children, Am. J. Dis. Child. **11**:432 (June) 1916.

DISCUSSION OF THE PATHOLOGIC FINDINGS

The resemblance between the clinical findings in this case and those of chronic diffuse nephritis was marked. The clinical findings in both types of cases were determined by the extreme impairment of renal function but the kidney lesions were very different anatomically.

In the majority of cases considered in a previous paper [1] the pathologic findings in the kidney were similar to those found in the primary diffuse nephritis of adults. In the present case, the kidneys present a different pathologic picture. The sections were remarkable because of the marked dilatation of the tubules. This dilatation was general but was most marked in the peripheral half of the organ. In this peripheral zone the convoluted tubules assumed enormous proportions. They appeared as large, irregular, open spaces lined with epithelium, essentially cuboidal in type, and in a fair state of preservation. In these areas of tubular dilatation the interstitial tissue was practically insignificant and a picture not unlike lung tissue was formed. Most of the spaces contained coagulated fluid but a few cellular casts were seen. In the cortex the glomeruli showed great increase in size. The majority of the largest ones appeared close to the capsule of the kidney, but the glomerular hypertrophy was general. Signs of chronic inflammation, for the most part interstitial in character, were present throughout the entire section. It was most prominent close to the capsule where there was a peripheral zone of marked round cell infiltration and fibrosis. The glomeruli themselves escaped direct involvement other than thickening of the capsule of Bowman. Through the zone of dilatation this inflammatory reaction was not marked, but in the region of the papillae there again was diffuse, round cell infiltration, and some interstitial fibrosis. Some of the papillary tubules showed epithelial proliferation. A few of them contained red blood cells but other signs of an acute nephritis were lacking.

The appearance of the zone of dilated tubules suggested that this was a case of early congenital cystic kidney. Congenital cystic kidney is found under widely varying circumstances and an extensive literature has arisen concerning the mode of origin of the cysts. Numerous theories have been proposed to explain the development of the polycystic kidney but at present only two are seriously accepted: (1) the theory that the process is due to a neoplasm; (2) the theory that the process is due to congenital malformation. Various combinations of these two theories have also been proposed.

The older theory of Virchow [14] has been discarded completely. He assumed that the cysts in congenital cystic kidney were retention cysts

14. Virchow, R.: Ueber congenitale Nierenwassersucht, Ges. Abhandl. z. Wissench. Med. Frankfurt, 1856, p. 864.

of inflammatory origin. Following an intrauterine papillitis or nephritis, the proliferation of scar tissue caused an obliteration of the collecting tubules with resultant cyst formation. Busse [15] and Berner,[16] in particular, have pointed out that the proliferation of the interstitial tissue is secondary to the cystic changes. In addition, Petterson [17] produced an experimental obliteration of the collecting tubules in rabbits by ligating the renal papilla. This resulted in a temporary dilatation of the entire tubule followed by atrophy. Tollens [18] found similar atrophy and destruction of the tubules following cauterization of the papilla.

Brigidi and Severi [19] first brought the theory of new growth into prominence. They observed epithelial proliferation in the tubules and the formation of epithelial nests which became converted into cysts by secondary degenerative changes. Papillary outgrowths from the epithelium of the dilated tubules were also observed. The changes in the kidney showed marked similarity to those occurring in cystadenomas of the ovary. Because of this the renal lesion was classified as a true neoplasm. Nauwerck and Hufschmid [20] emphasized the evidence of new growth associated with congenital cystic kidney. They recognized buds from the tubules, intracystic papillary growths, and the development of epithelial cell nests. With Von Kahlden [21] they emphasized the frequent association of cystic changes in the liver with cysts in the kidney. Von Kahlden, in particular, thought the changes in the liver were due to the adenoma or cystadenoma of the bile passage and the association of this condition with similar changes in the kidney spoke very strongly for the identity of the pathologic process involved in both instances.

In two cases of congenital cystic kidneys and liver occurring in infants Bunting [22] showed that there was a condition of hyperplasia of the duct epithelium with a tendency to cyst formation. This was most marked in the kidneys and liver but occurred to a less degree in the pan-

15. Busse, O.: Ueber Cystenniere und andere Entwicklungsstörungen der Niere, Arch. f. path. Anat. u. Physiol. **175**:442, 1904.

16. Berner, O.: Zur Zystennierenfrage, Arch. f. path. Anat. u. Physiol. **211**: 265, 1913.

17. Petterson, A.: Ueber die Veränderungen der Niere nach Läsion der Papille beim Kaninchen. Beitr. z. path. Anat. u. z. allg. Path. **33**:605, 1903.

18. Tollens: Ueber die Folgen der Markkegelobliteration der Kaninchenniere, Arch. f. path. Anat. u. Physiol. **177**:477, 1904.

19. Brigidi, V., and Severi, A.: Contributo alla pathogensi delle cisti renale, Lo Sperimentale **46**:1, 1880.

20. Nauwerck, C., and Hufschmid, K.: Ueber das multiloculare Adenokystom der Niere. Ein Beitrag zur Kenntniss der Cystenniere, Beitr. z. path. Anat. u. z. allg. Path. **12**:1, 1893.

21. Von Kahlden, C.: Ueber die Genese der multiloculären Cystenniere und der Cystenleber, Beitr. z. path. Anat. u. z. allg. Path. **13**:291, 1893.

22. Bunting, C. H.: Congenital Cystic Kidney and Liver with Family Tendency, J. Exper. M. **8**:271, 1906.

creas. Bunting found some increase in the number of tubules but there was no sharp distinction between abnormal tubules and normal renal parenchyma. The evidence of epithelial hyperplasia was widespread, and Bunting did not think the diagnosis of adenocystoma justified. The familial character of his two cases lead him to a diagnosis of congenital malformation rather than of neoplasm.

The familial and hereditary occurrence of congenital cystic kidney has been noted by many authors since the time of Virchow. Not only are congenital cystic kidneys frequently familial in origin but a long series of associated congenital malformations have been reported. Dunger [23] and Meyer [24] have both reviewed this literature in detail.

The explanation of the mechanism for the origin of congenital cystic kidney as a congenital malformation have varied greatly with the conception of the normal development of the kidney current at the time. Hildebrand [25] made use of the modern dualistic theory [26] of the formation of the permanent kidney. He postulated a failure of union between the collecting and convoluted tubules. The cysts were assumed to be retention cysts developing in the glomeruli and convoluted tubules. Ribber [27] assumed the same type of developmental defect of the tubules but emphasized the importance of proliferative changes in the epithelium in their relation to cyst formation. This explanation of the mechanism of cyst formation has received much support from the reconstructions of the tubules from cases of congenital cystic kidney made by Meader [28] and Forssman.[29]

Meader found glomeruli without uriniferous tubules, glomeruli with dilated capsules but no outlets, and glomeruli opening into short uriniferous tubules which ended in cysts. Study made clear that the glomerulus and the proximal portion of the uriniferous tubule were the parts involved in his case, but Meader did not feel justified in drawing conclusions as to the mechanism responsible for the lesion. Forssmann agreed with Hildebrand in thinking that the cysts were retention

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23. Dunger, R.: Zur Lehre von der Cystenniere mit besonderer Berücksichtigung ihre Heredität, Beitr. z. path. Anat. u. z. allg. Path. **35**:445, 1904.

24. Meyer, E.: Ueber die Entwicklungstörungen der Niere, Arch. f. path. Anat. u. Physiol. **173**:209, 1903.

25. Hildebrand, O.: Weiterer Beitrag zur pathologischen Anatomie der Nierengeschwülste, Arch. f. klin. Chir. **48**:343, 1894.

26. Felix, W.: The Development of the Urinogenital Organs, Manual of Human Embryology (Keibel and Mall), Philadelphia **2**:752, 1912.

27. Ribbert, H.: Ueber die Entwicklung der bleibenden Niere und die Enststehung der Cystienniere, Verhandl. d. deutsch. path. Gesellsch. **2**:187, 1900.

28. Meader, F. M.: A Study of the Anatomical Relations in a Congenital Cystic Kidney, Johns Hopkins Hosp. Bull. **18**:353, 1907.

29. Forssman, J.: Rekonstruktionen von Cystennieren, zugleich ein Beitrag zur Kenntnis der Entstehung von Cystennieren, Beitr. z. path. Anat. u. z. allg. Path. **56**:500, 1912.

cysts. The proliferative changes in the epithelium are striking in many instances and Staemmler [30] among others, admits the developmental defect in the tubule but insists that the secondary changes are neoplastic in character. McKinley [31] has recently reviewed the subject of the epithelial changes in cystic kidney. He emphasized the similarity of the changes to those seen in compensatory hyperplasia of the kidney from other causes and suggested that the changes in the epithelium were expressions of compensatory effort in an organ whose functional capacity had been reduced by primary cystic changes.

Failure of union of the two separate elements of the renal anlage will not explain the origin of all cases of cystic kidney. Von Mutach [32] and Bunting,[22] by a study of serial sections, were able to prove the continuity of the renal tubules in the cases reported by them. Berner [33] also found carmine in the cysts after its injection into the ureter. In all of these cases well developed cysts were present. Retention alone will not suffice to explain the origin of the cysts.

In order to study the true pathologic picture in the present case, the kidney tubules were modeled by the well known wax plate reconstruction method. Distortion of the sections by the dilatation of the tubules made reconstruction difficult but it was usually possible to follow any tubule through part of its course and several were followed through greater distances. The kidney was also studied by digestion in hydrochloric acid and dissection of the individual tubules.[34]

The glomeruli were large and showed very little change although the tuft seemed to be somewhat looser and less compact than normal and the glomerular capsule was slightly distended. The changes in the tubules varied slightly in the different parts of the kidney but, in general, the first portion of the proximal convoluted tubule was only slightly dilated. Its epithelium was cuboidal and somewhat swollen and granular. The changes in the tubule first became striking in the second portion of the proximal convoluted tubule. This portion of the tubule was distorted out of all recognition by a series of large cystic dilatations. For the most part these dilatations approached the spherical although some were fusiform in shape. The epithelium of these cysts was primarily cuboidal although in many places it was

30. Staemmler, M.: Ein Beitrag zur Lehre von der Cystenniere, Beitr. z. path. Anat. u. z. allg. Path. **68**:22, 1921.

31. McKinlay, C. A.: Epithelial Hyperplasia in Congenital Cystic Kidneys, J. Urol. **4**:195, 1920.

32. Von Mutach, A.: Beitrag zur Genese der congenitalen Cystennieren, Arch. f. path. Anat. u. Physiol. **42**:46, 1895.

33. Berner, O.: Die Cystenniere, Jena, 1913.

34. I am indebted to Dr. W. G. MacCallum for suggesting this use of reconstruction methods in the study of the pathology of the tubule, and for much criticism and advice in the course of this study.

flattened as a result of distention or pressure. The epithelium was granular and in some of the cysts had become completely degenerated, filling the tubule with granular debris. Intercommunication between these saccular dilatations was for the most part quite free although in some cases there was constriction by intervening bands of interstitial fibrous tissue.

This dilated portion of the tubule occupied the outer fourth or fifth of the kidney. The loops of Henle were of nearly uniform caliber throughout. The ascending limb of the loop of Henle and the distal convoluted tubule occasionally showed slight dilatation but this did not approach the cystlike character observed in the proximal convoluted tubules. The majority of the tubules showed well developed loops of Henle and opened into a collecting tubule in the usual manner. In others there was no loop of Henle and the descending portion of the tubule opened directly into the collecting tubule in the vicinity of the pelvis. The structure of these latter tubules was very suggestive of the type of embryonic tissue described by Traut.[35] Both types of tubule showed much the same degree of cystic dilatation and apparently were equally affected by the pathologic process.

The cysts in the kidney were not retention cysts for the changes in the tubules were changes in form and not of structure. There was no evidence of the type of developmental defect in the tubules that is reported as associated with congenital cystic kidney. Hydronephrosis follows obstruction in the urinary tract but this is associated with atrophy and not with dilatation of the individual tubules.

The kidneys in the present cases were remarkable because of their small size. All degrees of failure in the renal anlage have been described, from complete absence of the kidney to relative hypoplasia on the one side or the other. Cystic change is present in such rudimentary kidneys as in the case reported by Sternberg[36] and there is no sharp distinction between that condition and the hypoplastic cystic kidneys reported on by Von Mutach, Staemmler, or Schaefer.[37]

In the present case the kidneys were greatly reduced in size and the cortex was much thinner than normal. The glomeruli were greatly reduced in numbers. No attempt was made at enumeration but it is evident that there was but a fraction of the normal number of renal tubules present. The kidneys present some slight evidence of inflam-

35. Traut, H. F.: Personal communication to the author. I am greatly indebted to Dr. Traut for his dissection of the tubules and confirmation of the author's findings in this case.

36. Sternberg, C.: Zur Kasuistik der Nierendefekte und Miszbildungen des Urogenitalapparates, Wien. klin. Wchnschr. **20**:130, 1907.

37. Schaefer, F.: Ueber eine hypoplastiche und eine partielle Zystenniere, Frankfurt. Ztschr. f. Pathol. **26**:128, 1921.

matory changes but this does not explain the reduction in the number of tubules. Particularly striking is the absence of atrophic changes in the tubules, especially when this kidney is compared with one from a case of chronic diffuse nephritis. The small size of the kidneys is due to a failure in development rather than to degeneration or atrophy of these organs. Clinically this case presented evidences of a marked renal insufficiency. The tubules showed some evidences of epithelial hyperplasia though this was never extreme and there were no papillomatous changes. McKinlay has pointed out that such changes are to be interpreted as a compensatory hyperplasia consequent to the renal insufficiency. The dilatation of the convoluted tubules must likewise be considered as an active process associated with functional hypertrophy.

SUMMARY

A case is reported of congenital cystic kidney in a girl, aged 3 years. The clinical findings were the same as occur in chronic diffuse nephritis of congenital origin. The pathologic picture was that of bilateral hypoplasia of the kidneys with cyst formation. The renal tubules were characterized by marked cystlike dilatations, especially in the proximal convoluted tubules. There was no evidence of obstruction and the dilatation apparently was secondary to functional hypertrophy of the tubules. It should be emphasized that the clinical picture was determined by the functional insufficiency rather than by the pathologic changes in the kidney.

ULTRAVIOLET RADIATION IN RICKETS

EFFECT ON THE CALCIUM AND INORGANIC PHOSPHORUS CONCENTRATION OF THE SERUM *

B. KRAMER, H. CASPARIS AND J. HOWLAND

BALTIMORE

Huldschinsky [1] has shown conclusively that when children suffering from rickets are exposed repeatedly to the rays of the mercury vapor quartz lamp, healing of the rachitic process ensues. The changes were demonstrated by means of roentgenograms. The work has been amply confirmed by others. Howland and Kramer [2] have reported the observation that the inorganic phosphorus of the serum is markedly reduced in uncomplicated rickets and that the concentration of this substance rises to normal or slightly above normal limits following the regular administration of cod liver oil. Iversen and Lenstrup [3] have made a similar observation with regard to the acid soluble phosphorus of the plasma. In a previous paper [2] the importance of a normal inorganic phosphorus concentration for the orderly progress of calcification has been emphasized. McCollum, Park and their associates have produced rickets in rats by administering a diet containing an excess of calcium but deficient in phosphorus and the unidentified antirachitic factor present in cod liver oil. Analyses by Kramer and Howland [5] have shown that the concentration of inorganic phosphorus in the serum of such animals is reduced far below the normal level, while the calcium concentration remains normal. The concentrations of calcium and of inorganic phosphorus in the serum of these animals and in those of children suffering from rickets are essentially the same. Exposure of such animals to ultraviolet light, whether emanating from the mercury

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* From the Harriet Lane Home and the Department of Pediatrics, The Johns Hopkins University.

1. Huldschinsky, K.: Heilung von Rachitis durch künstliche Höhensonne, Deutsch. med. Wchnschr. **45**:712 (June) 1919. Die Behandlung der Rachitis durch Ultraviolett Bestrahlung, Ztschr. f. orthop. Chir. **39**:426, 1920.

2. Howland, J., and Kramer, B.: Calcium and Phosphorus in the Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

3. Iversen, P., and Lenstrup, E.: Förste Ved. Nordiske Kongres for Paediatri, 1919, p. 79.

4. McCollum, E. V.; Simmonds, N.; Shipley, P. G., and Park, E. A.: Studies on Experimental Rickets. VII. The Production of Rickets by Diets Low in Phosphorus and Fat-Soluble A, J. Biol. Chem. **47**:507 (Aug.) 1921.

5. Kramer, B., and Howland, J.: The Influence of Diet on the Concentration of Phosphorus and Calcium in the Serum of Rats, Proc. Soc. Biol. Chem. **5**:21, 1921. Howland, J., and Kramer, B.: Factors Concerned in the Calcification of Bone, Proc. Am. Pediat. Soc., 1922.

vapor quartz lamp, the cadmium spark, or the ferric chromium condenser spark results in an increase of the inorganic phosphorus of the serum and the appearance of fresh deposits of calcium in the bones. The changes are identical with those which occur in rachitic children when cod liver oil is administered. In a recent communication Gutman

Fig. 1.—Radius and ulna of G. W. (Case 1) before (Jan. 31) treatment; thirty days after (March 7) treatment, and forty-four days after (March 21) treatment.

and Franz [6] state that they have found an increase in the inorganic phosphorus of whole blood of rachitic rats after exposure to ultraviolet rays. Hess and Unger [7] report the cure of rickets in children and the

6. Gutman, M. B., and Franz, V. K.: Observations on the Inorganic Phosphate of Blood in Experimental Rickets in Rats, Proc. Soc. Exper. Biol. & M. **19**:171, 1922.

7. Hess, A. F., and Unger, L. J.: Use of the Carbon Arc Light in the Prevention and Cure of Rickets, J. A. M. A. **78**:1596 (May 27) 1922.

prevention of rickets in rats by means of a carbon arc light. They report also a slight increase in the inorganic phosphorus of the blood of children so treated.

The observations with children that we have to report were made as a continuation of our observations on rachitic animals. Radiation was accomplished by means of a mercury vapor quartz lamp. The spectrum of the light from this lamp showed in addition

Fig. 2.—Tibia and fibula of R. H. (Case 2) before (Jan. 18) treatment; forty-two days after (March 7) treatment and fifty-six days after (March 21) treatment.

to the rays of longer wave length, bands of considerable intensity in the second ultraviolet region (from 2,900 to 1,850 Aengstrom units). Of these, rays having a wave length of about 2,560 Aengstrom units gave the most intense band.

Five children, four colored and one white, were treated by these rays. They were exposed at a distance of 50 cm. every day, at first for five minutes and then the length of exposure was rapidly increased

to twenty minutes. On alternate days the ventral and dorsal aspects of the body were radiated. The eyes were carefully protected. The amount of current employed was 8 ampères.

Roentgenograms were made before and several times during the course of treatment. Determinations of the calcium and inorganic phosphorus of the serum were made at least three times with each patient, once before and twice during treatment.

SUMMARY

Five children showing clinical evidences of rickets, confirmed by roentgenographic examination of the bones, were treated by systematic exposure to the rays from the mercury vapor quartz lamp. This was followed in every instance by healing of the rachitic process in the bones. The inorganic phosphorus concentration of the serum of these children was low (from 2.7 to 3.2 mg.) before the treatment was begun and gradually increased to a maximum of 6 mg. with the appearance of calcium deposition in the bones. So far as could be judged, healing of the bones following radiation occurred at about the same time as it does after the administration of cod liver oil. The changes in the phosphorus concentration of the serum were identical with those observed after cod liver oil treatment. The pigmented skin of the negro child did not interfere with the action of the light rays. The colored children required no more intensive treatment to bring about healing than did the white children.

REPORT OF CASES

Case 1.—G. W., white, aged 7 months, a premature child; evidence of rickets not marked.

Jan. 31, 1922: Roentgenogram showed slight irregularity of extremities of radius and ulna.

February 2: Calcium, 8.5 mg. per 100 c.c. of serum; inorganic phosphorus, 3 mg.

February 5: Treatment begun.

March 7: Roentgenogram showed marked irregularity of lower extremities of radius and ulna, evidently brought about by considerable deposition of lime salts. This had produced distinct cupping.

March 8: Calcium, 10.1 mg. per 100 c.c. of serum; inorganic phosphorus, 5.8 mg.

March 21: Roentgenogram showed evidences of healing still more marked.

March 21: Calcium, 10.3 mg. per 100 c.c. of serum; inorganic phosphorus, 6 mg.

Case 2.—R. H., colored, aged 10 months; marked clinical evidences of rickets.

Jan. 18, 1922: Roentgenogram showed very severe rickets. Centers of ossification poorly marked. Extremities of bones very indistinct.

January 21: Calcium, 9.4 mg.; inorganic phosphorus, 2.7 mg.

January 24: Treatment begun.

March 7: Roentgenogram showed evidences of deposition of lime salts producing double lines at extremities of bones. Centers of ossification becoming plain.

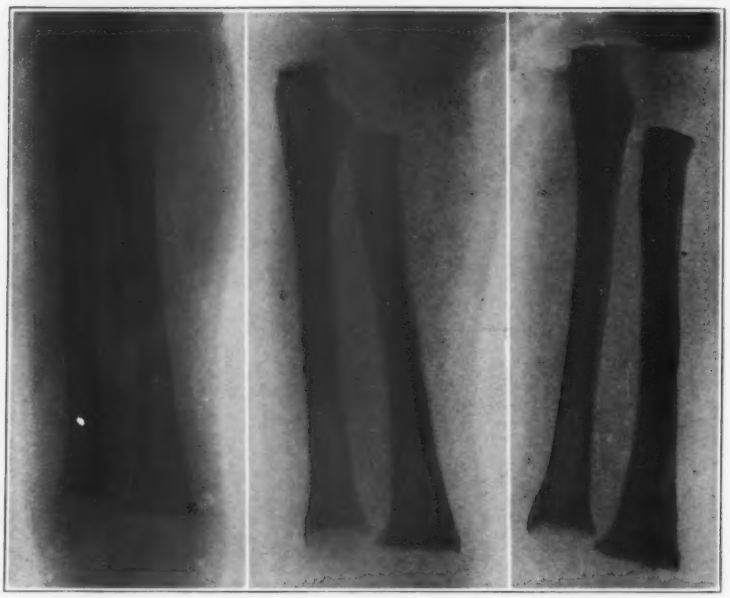

Fig. 3.—Tibia and fibula of E. F. (Case 3) before (Feb. 2) and forty-three days after (March 21) treatment.

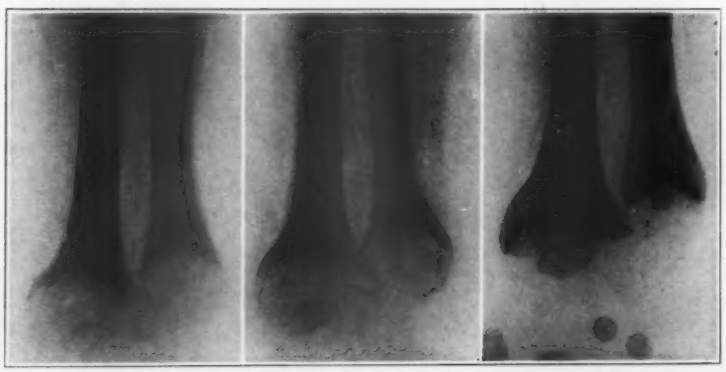

Fig. 4.—Radius and ulna of F. P. (Case 4) before (Jan. 16) treatment; twenty-seven days after (Feb. 20) treatment, and forty-two days after (March 7) treatment.

March 8: Calcium, 9.3 mg.; inorganic phosphorus, 3.4 mg.
March 21: Roentgenographic evidences of healing plain.
March 21: Calcium, 10.1 mg.; inorganic phosphorus, 6.2 mg.

CASE 3.—E. F., colored, aged 26 months; marked clinical evidences of rickets.

Feb. 2, 1922: Roentgenogram showed striking evidences of rickets of long standing.
February 6: Calcium, 10.6 mg. per 100 c.c. of serum; inorganic phosphorus, 3 mg.
February 6: Treatment begun.
March 21: Roentgenogram showed marked evidences of healing. Deposition of lime salts at extremities of bones now plain.
March 22: Calcium, 9.5 mg.; inorganic phosphorus, 6 mg.

CASE 4.—V. P., colored, aged 18 months; marked clinical evidences of rickets.

Jan. 16, 1922: Roentgenogram showed cupping of lower ends of both radius and ulna. Centers of ossification at wrist indistinct.

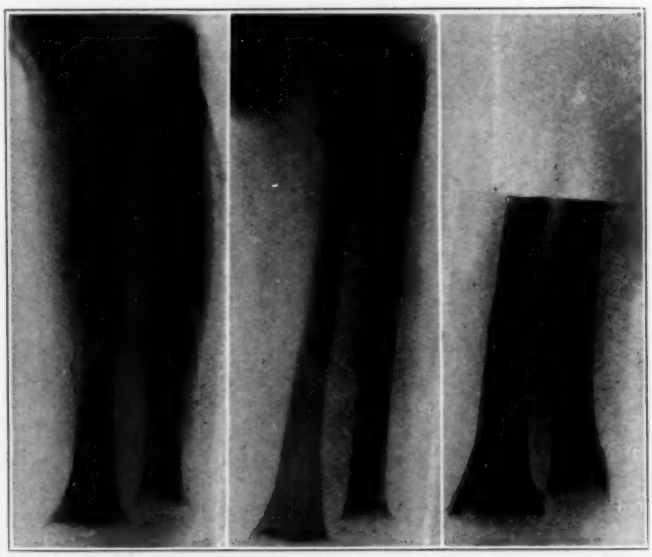

Fig. 5.—Radius and ulna of M. C. (Case 5) before (Dec. 20) treatment; after forty days (Jan. 30) insufficient treatment, and after forty-nine days (March 21) intensive treatment.

January 18: Calcium, 9.2 mg. per 100 c.c. of serum; inorganic phosphorus, 3 mg.
January 24: Treatment begun.
February 20: Roentgenogram showed early but definite evidences of healing.
February 23: Calcium, 10.1 mg.; inorganic phosphorus, 4.6 mg.
March 7: Roentgenogram showed marked evidences of healing.
March 8: Calcium, 10.2 mg.; inorganic phosphorus, 6.6 mg.

CASE 5.—M. C., colored, aged 5 months. Clinical diagnosis on admission was rickets and tetany.

Dec. 20, 1921: Roentgenogram showed mild but definite rickets. Cupping at lower end of the ulna, irregularity of the lower end of the radius.
December 21: Calcium chlorid was administered, 1 gm. every four hours, for several days. It was then reduced to 0.5 gm. Radiations with ultraviolet

rays were also employed. The time of exposure was short (from 5 to 10 minutes); the intensity was slight (amount of current, 4 amperes) and the child was exposed only three times a week.

Jan. 21, 1922: Calcium, 8 mg. per 100 c.c. of serum; inorganic phosphorus, 3.2 mg.

January 30: Roentgenogram showed no change.

February 1: As it was obvious that no improvement had taken place more intensive treatment was employed as outlined in the first part of the paper.

February 27: Roentgenogram showed definite evidence of healing.

March 6: Inorganic phosphorus, 6.2 mg.

March 21: Roentgenogram showed almost complete healing.

March 21: Calcium, 9.8 mg.; inorganic phosphorus, 6.1 mg.

THYMUS APOPLEXY

AN UNUSUAL MANIFESTATION OF HEMORRHAGIC DISEASE OF THE NEWLY BORN *

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The thymus gland is richly supplied with blood vessels [1] which are readily engorged and often contribute considerably to the enlargement of the gland.[2] This congestion is especially apt to occur whenever there is a general circulatory stasis.[3] There is little supporting tissue for the rich network of capillaries in and about the individual lobules so that hemorrhages occur readily.[3] These may be scattered, small and petechial in character, or they may appear as large effusions of blood localized or diffused throughout the substance of the organ. The former are common, especially in asphyxial conditions, in acute infections and in hemorrhagic diseases. The latter are relatively rare and were first noted by Friedleben [4] in his basic monograph in which he applied the term "Apoplexien" to these more extensive hemorrhages. Such an "apoplexy" may follow the hyperemia associated with simple hyperplasia of the gland and may give the appearance of a hemorrhagic infarct.[5] Inasmuch as but few cases are in the literature a review of these is given.

Friedleben [4] noted the occurrence of these extensive hemorrhages in the thymus gland in cases of protracted and difficult labor and regarded them as traumatic in origin. He also gave a detailed description of a 5 month old infant which died suddenly during convalescence from an attack of diarrhea. The infant had taken its bottle during the night and was found dead in the morning. The necropsy showed subserous hemorrhages in the pleura and pericardium. The thymus gland was diffusely infiltrated with blood. No microscopic examination was made.

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* From the Departments of Pathology and Pediatrics, University of Kansas School of Medicine.

1. Pigache, R., et Worms, G.: Circulation du lobule thymique, Bull. et mém. soc. Anat. de Par. **12**:837, 1910.
2. Hart, C.: Thymus Studien: Pathologie der Thymus, Arch. f. path. Anat. **214**:1, 1913.
3. Wiesel, J.: Pathologie des Thymus, Ergebn. der allg. Path. u. path. Anat. **15**: Pt. 2, 416, 1912.
4. Friedleben, A.: Die Physiologie der Thymusdrüse in Gesundheit und Krankheit, Frankfurt A. M. Literarische Anstalt. 1858.
5. Marfan, A. B.: Pathologie du Thymus, Arch. de méd. d. enf. **13**:801, 1910.

Several cases are cited by some authors with such meagre data that their value is doubtful. Raudnitz [6] cites the case of a child, 5 months old, dying with asphyxial symptoms. At the necropsy there was a large thymus, infiltrated with blood. He also cites Kopp's case of an infant 33 days old, with hemorrhages from the umbilicus, dying nine days later. The postmortem examination showed a pneumonia, a bloody effusion about the umbilicus and a bloody tumor mass covering the upper anterior surface of the heart and containing thymus elements. Both Friedleben [4] and Wiesel [3] note Weber's case of a several months' old infant dying after several severe abdominal cramps. The necropsy showed a fresh hemorrhage in the thymus gland. Wiesel also cites Bonnet's case occurring in a man who died suddenly and in whom the thymus gland was found enlarged and infiltrated with blood. The same author mentions Beneke's case occurring in the stillbirth in which the fetus was forcibly extracted. There was a hemorrhage in the thymus and also over the surface of the brain. Bauer's case is also cited. The patient was a young soldier who died suddenly without any apparent cause. The thymus gland was found infiltrated with blood.

Barensprung [7] described the case of an infant which was struck by its syphilitic mother the day after its birth, and had hemorrhages from the navel and ecchymoses in the shoulders, arms and hands. Death occurred eight days after birth. The necropsy showed numerous subcutaneous hemorrhages, especially in the cheek, and on the hands and chest. The umbilical vein was occluded by a thrombus. The thymus was very large and infiltrated with blood, and also contained a cavity filled with a soft red blood clot. There was also a bloody fluid in the pericardium and focal hemorrhages in the kidney medulla. The latter also contained uric acid infarcts.

Raudnitz [6] reported two cases. One patient was an infant with a syphilitic mother. Following birth a hematoma developed over the right parietal bone. The infant was jaundiced but otherwise was apparently well to the forty-fifth day when it suddenly became pale, respirations were rapid, pulse 120 and hemorrhages appeared in the hard palate. The child refused food. Vomiting occurred and was followed by collapse and death. Blood clots were found in the occipital and temporal fossae. The left pleural cavity contained much clotted blood. The mesenteric glands were enlarged and contained hemorrhages. The left lobe of the thymus was enlarged, measuring 5 cm. in length, and contained extensive hemorrhages. The right lobe was normal.

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6. Raudnitz, R. W.: Hemorrhagien der Thymus, Arch. f. Kinderh. **4**:21, 1883.
7. v. Barensprung, F.: Die Hereditare Syphilis, Berlin, 1864.

The second case was that of an infant showing blood in the stools and punctate hemorrhages in the palate when ten days old. Dyspnea then developed, followed by death five days later. The necropsy showed a blood clot over the left cortex and the pia was infiltrated with blood. Hemorrhages were present in both lower lobes of the lungs, in the pericardium and in the tissue about the thymus and adjacent esophagus. The left lobe of the thymus was enlarged and contained a hematoma the size of a walnut.

Durante [8] also described two cases. In the first case the infant was born dead following a protracted labor. The thymus gland was enlarged, weighing 21 gm. The gland showed intense congestion and also hemorrhages, especially within the lobules, in some of which the entire medullary substance was so extensively replaced by blood that only a narrow rim of cortical substance remained. The blood was not collected in a single continuous mass but diffusely infiltrated the gland, separating the architectural elements.

The second case was in a premature child which died suddenly on the fourth day without any apparent cause. The thymus gland was enlarged, weighing 20 gm. There were numerous hemorrhages some of which destroyed several lobules. Some of the foci infiltrated with blood showed organization indicating that some of the effusions of blood were older than others.

Schlesinger [9] described a hemorrhage in the thymus gland, occurring in a syphilitic infant who had a persistent umbilical hemorrhage from which it died on the ninth day. The necropsy showed fibrous induration of the lungs, liver and pancreas, indicating congenital syphilis. The thymus gland was enlarged and on the left side contained a small cavity filled with clotted blood. In addition there were several smaller hemorrhages in the tissue surrounding the larger one. These hemorrhages involved the parenchyma and the stroma but the medullary substance showed more disintegration than the cortex. Hassall's corpuscles were numerous and persisted even in the masses of blood when all other thymus elements had disappeared. Focal necroses were also present.

Mendelsohn [10] contributed the most complete discussion of this subject and gave a detailed description of a thymus hemorrhage occurring in a syphilitic infant dying five hours after birth. There was a pemphigous eczema on the soles of the feet and the palms of the hand.

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8. Durante, G.: Hemorrhages et scleroses due thymus chez les enfants nouveau-nes, Compt. rend. Soc. de biol. **48**:282, 1896.

9. Schlesinger, E.: Die Erkrankungen der Thymusdrüse bei der hereditaren Syphilis, Arch. f. Kinderh. **26**:205, 1899.

10. Mendelsohn, L.: Ueber die Apoplexie der Thymusdrüse, Arch. f. Kinderh. **44**:1, 1906.

The lungs were indurated and the liver enlarged. The thymus gland weighed 8.7 gm. The left lobe was normal. The right lobe contained a cavity about the size of a hazelnut filled with partly clotted blood. There were also a few smaller hemorrhages. Microscopic examination showed typical syphilitic changes in the lungs and the liver. The vessel walls were thickened, especially the adventitia. The wall of the blood containing cavity was composed of three layers, the inner one only being composed of thymus elements. This cavity was a preformed cyst into which a hemorrhage had occurred.

Winkler [11] reported a case occurring in a male infant which was well at birth, but developed dyspnea, cyanosis and cardiac weakness, and finally death ensued on the fourth day. There was a subpial hemorrhage on the right side. The thymus gland was enlarged and on section showed many hemorrhages uniformly distributed throughout the gland.

Klose [12] described a diffuse hemorrhagic infiltration of the thymus gland in a boy, 9 years old, who had whooping cough and died from asphyxia following a severe paroxysm of coughing. The gland was much enlarged. No other hemorrhages were noted. A tracheotomy was performed but was of no avail.

Hart [2] noted a case of diphtheritic laryngitis in which the thymus gland was entirely hemorrhagic and infarcted.

Pappenheimer's case [13] occurred in a 7 week old syphilitic infant who had a general purpuric eruption, an interstitial pneumonia and a well marked status lymphaticus. The thymus gland was enlarged, weighing 25 gm., and was diffusely infiltrated with blood. There were also extensive areas of necroses. The cytoplasm of the reticular cells contained yellow pigment granules. The small thymus elements were not abundant. There were no Hassall's corpuscles. The parenchyma was composed mostly of large reticular epithelial cells with indifferent cell outlines and extensive intercellular connections. The usual lobulation of the thymus gland was absent. There was evidently a delay in the development of the gland.

The last case reported was that of Frazier [14] in which the thymus of a syphilitic male stillbirth was enlarged and contained scattered hemorrhages. The upper half of the gland contained a spherical cavity, the size of a dime, distended with fluid blood. In the lower half there

11. Winkler: Zur Pathologie der Thymusdrüse, Verhandl. d. deutsch. path. Gesellsch. **13**:266, 1909.

12. Klose, H.: Chirurgie der Thymusdrüse, 1912, in Frankfurt a. M.

13. Pappenheimer, A.: A Contribution to the Normal and Pathological Histology of the Thymus Gland, J. M. Research **22**:1, 1910.

14. Frazier, J. F.: The Visceral Changes in Congenital Syphilis, J. A. M. A. **77**:1623 (Nov. 19) 1921.

was a cavity the size of a quarter containing grayish white purulent matter. There was no cyst formation. There were multiple granulomas in the cortex.

An analysis of the nineteen cases found in the literature is interesting. It is probable that more cases have been reported but are buried under general and obscure titles. In fact, only five cases of this series were reported under a specific title while the remainder were gleaned from papers on either the pathology of the thymus gland or congenital syphilis. A small proportion only (seven cases) had a complete description. In some of these a thorough microscopic study was not made. In all cases but two there was a note on the nature of the hemorrhage. In eleven cases it was diffused throughout the gland; in the remainder it was localized to one or more foci. The age was noted in all but one of the cases and varied from stillbirths to young adults. Three cases occurred in stillbirths, three in infants less than one week old; six infants were between this age and 3 months; three cases occurred between 3 and 6 months, one child was 9 years of age and two patients were young male adults. It is worth emphasizing that with the exception of three cases, two of which occurred in young men, all the other cases occurred in infants under 6 months.

The nature of the death was noted in thirteen cases. In seven cases it was sudden, but no other information was available. In two instances it followed persistent hemorrhages. In two cases there was dyspnea; in two, asphyxia, and in one case severe cramps. The presence or absence of other hemorrhages was not noted in eight cases; in three cases they were absent; in two cases there were hemorrhages in the umbilicus; in five cases, subserous hemorrhages, and in five cases cerebral hemorrhages were associated.

Regarding the presence of visceral lesions no information was available in ten of the cases. In two cases they were reported as being absent. In three cases an interstitial pneumonia was noted. One infant had pneumonia, one had diphtheretic laryngitis and another had lung infarcts. Regarding the possibility of syphilis being present no information was available in seven cases. In six cases a definite diagnosis of hereditary syphilis was made. In two instances there was a history suspicious of syphilis, In five cases it was absent. In five cases there was a history of trauma; in four cases it could be excluded, while in the others no note regarding trauma was made.

REPORT OF CASES

CASE 1.—Baby R., colored, male, aged 4 days, one of twins, was admitted to Bell Memorial Hospital, Sept. 19, 1920.

Family History.—Father, aged 43, living and well. Wassermann negative. Mother, aged 37, living and well. Three sisters, ages 8, 6 and 4 years, respectively, living. The eldest shows glandular enlargement and with questionable

Hutchinsonian teeth, but with a negative Wassermann. The youngest sister is markedly undernourished. There were two brothers. One aged 2 years had marked rickets and a negative Wassermann. The other was the twin brother of the patient and was apparently normal.

Past History.—During pregnancy the mother was unusually short of breath and had much distress. She felt that the baby was transverse in position. The pregnancy went to full term. The patient was the second born of twins and was delivered from a breech presentation with considerable traction and difficulty. On the second day the mother noticed bleeding from the mouth and persistent dark pasty stools. There were no convulsions. The infant fretted a great deal. The baby refused all food and was brought to the hospital on the fourth day with convulsions.

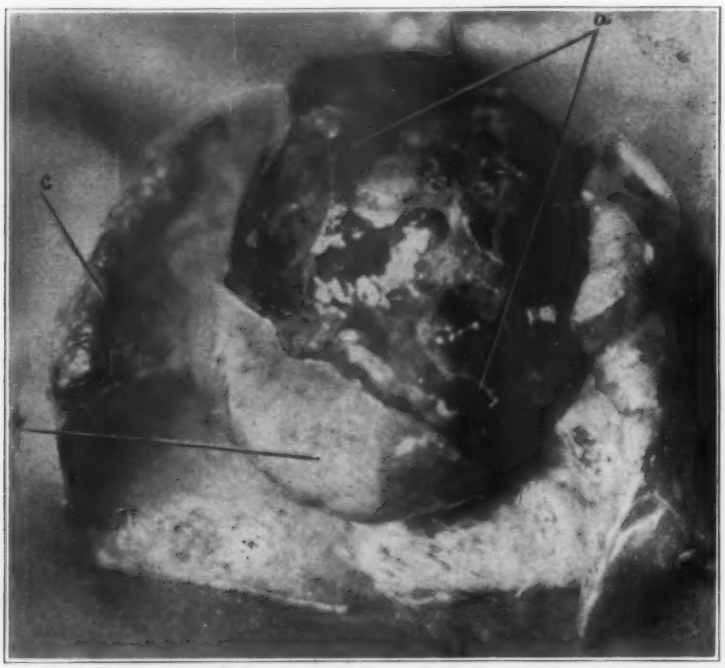

Fig. 1.—Photograph of the thymus gland of Case 2, showing its relation to the heart and to the lungs. (a) Thymus gland enlarged and infiltrated with blood; (b) apex of heart; (c) anterior edge of upper lobe of the right lung.

Physical Examination.—The baby was small and critically ill with a temperature of 102.5 F., and with the head drawn back. The arms and legs were very rigid and the fingers markedly flexed in a position of tetany. The skin and sclera showed a definite icterus. Clusters of miliary vesicles were present over the chest, neck and upper arms. Both fontanels were open but not depressed. There was no craniotabes or overriding of the cranial bones at the sutures. There was a lateral nystagmus of both eyes. Ears and nose were normal. The mouth could not be opened wide enough to inspect the throat, but the tongue was covered with a white milky coat. The heart was very rapid but no murmurs could be heard. The lungs showed no definite impairment. The breath sounds were very rapid and of a Cheyne-Stokes char-

acter. The abdomen was full and held very tense. The liver and spleen could not be felt. The genitalia were normal, except for phimosis. The lymph nodes were not prominent.

A puncture of the lateral ventricle was made through the anterior fontanel and 20 c.c. of unchanged blood was obtained. This blood clotted very slowly and the clot was soft in consistency. The red cells settled out. A Wassermann was done on this blood but was negative. The patient was moribund on entrance and died ten hours later.

Clinical Diagnosis.—Cerebral hemorrhage from a birth injury associated with hemorrhagic disease of the new-born.

Fig. 2.—Photomicrograph of a thrombus in a large vein of the thymus gland in Case 1. Note also the hemorrhage in the surrounding tissue and the endothelial hyperplasia in the small lymph node which is embedded in the capsule of the thymus gland.

NECROPSY REPORT

Macroscopic Examination.—The body is that of a well developed male infant showing generalized icterus, a fine vesicular eruption over the neck and chest and petechial hemorrhages on the buttocks. Bloody fluid is present in both pleural cavities, 30 c.c. on the right side, less on the left. There is a large red hemorrhagic mass with a smooth outer surface in the upper mediastinum extending from the lower border of the thyroid to the lower third of the pericardium and from the hilum of one lung to that of the other. It is composed mostly of an enlarged thymus diffusely infiltrated with blood, weighing 27.4 gm. and measuring 6x4x1.8 cm. The lobes of the thymus are indistinct. The mass is firm in consistency. The cut surface has a dark red color with a network of grayish white markings which give it a lobulated appearance. In some areas

the hemorrhage involves the parenchyma of the organ; in others it is limited to the stroma leaving islands of thymus tissue embedded in a mass of blood. The hemorrhagic infiltration extends into the soft tissues about the trachea, esophagus and hilum of the lung.

Hemorrhages were also present in other viscera. Scattered subpleural hemorrhages in the lungs extended a short distance into the substance of the lungs. Small hemorrhages were present in both the pericardium and in the myocardium. The kidneys showed numerous wedge shaped hemorrhages involving both cortex and medulla. Extravasations of blood were also present in the diaphragm along the attachment of the pericardium and in the medulla of both suprarenal glands. The cerebrospinal fluid over the surface of the brain was blood tinged. Both lateral ventricles were distended and dilated with

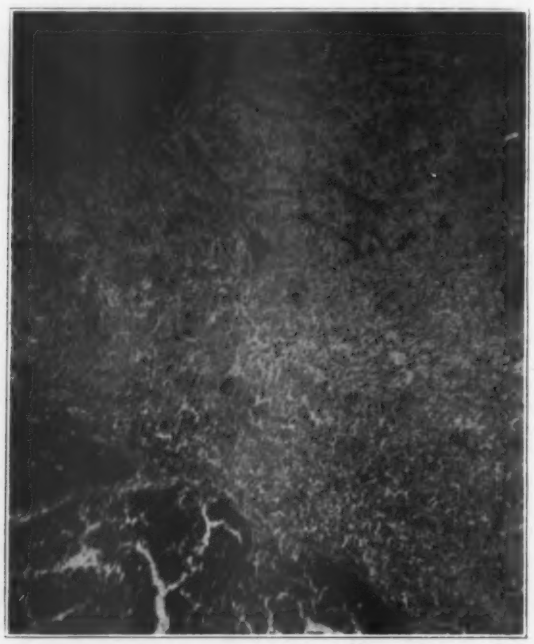

Fig. 3.—Photomicrograph of necrosis, hemorrhage and organization in the stroma of the thymus gland in Case 2. On each side of this thick band of connective tissue there are lobules of the thymus parenchyma infiltrated with red blood corpuscles.

bloody fluid. This was particularly true of the right lateral ventricle which contained 50 c.c. fluid blood in addition to a soft blood clot continuous with one in the left lateral ventricle which was nearly occluded by the blood clot. Fluid blood was also present in the other ventricles. The right parietal lobe was considerably softened due, in part, to the dilatation of the right lateral ventricle and, in part, to the extravasation of blood into the brain substance external to the posterior part of the right lateral ventricle.

Some portions of the lungs did not contain air. The consistency was tougher than usual. There was an unusually distinct lobulation. The foramen ovale of the heart was widely open. The liver showed some hemorrhages just beneath the capsule. Numerous brick red crystals (uric acid) were present in the pyramids of the kidneys.

Microscopic Examination.—Heart: Vacuoles are present in many of the muscle fibers. There are also small hemorrhages in the myocardium.

Lungs: Bands of cellular fibrous tissue subdivide the lung tissue into distinct lobules. The lung framework is markedly thickened and infiltrated with leukocytes, most of which are mononuclear in type. Small hemorrhages occur in the interstitial tissue especially about the hilum. The capillaries are engorged. The alveolar epithelial cells are swollen, small vacuoles are numerous in the cytoplasm of many cells and many others are desquamated into the alveolus. Red blood cells are present in some of the alveoli. Many air sacs contain desquamated epithelial cells and serum but relatively few leukocytes. The adventitia of the blood vessels is thickened and the lumen is often reduced in size.

Liver: The fibrous tissue is increased in the portal spaces. The liver cells are swollen and contain many small vacuoles. Various types of leukocytes are scattered throughout the lobule. A few eosinophil cells are also present. There are a few foci of myeloid cells in the sinusoids.

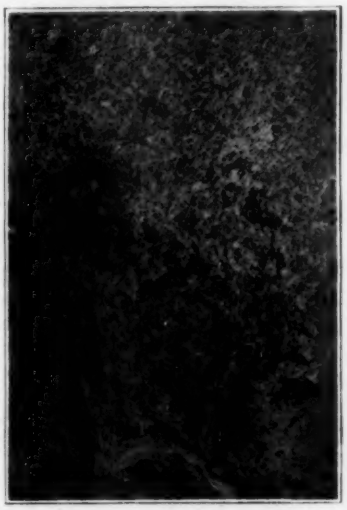

Fig. 4.—Photomicrograph of the perivascular inflammatory reaction and endothelioid hyperplasia in the stroma of the thymus gland in the second case.

Pancreas: The parenchyma is incompletely developed. Many of the acinar cells are degenerated. The islands of Langerhans are small and indistinct. The stroma is much more abundant than is usual.

Spleen: There is diffuse fibrosis throughout the pulp. The sinusoids are unusually prominent. There is marked endothelial hyperplasia. The walls of the vessels are thickened. The malphigian bodies are small and obscure.

Kidneys: They are infantile in type. The epithelial cells of some convoluted tubules are swollen and others are disintegrated. There is some proliferation and desquamation of the cells of the collecting tubules. The glomeruli are numerous. There are no red blood cells in the capillaries of the glomeruli. The endothelial cells of the latter are swollen. The interstitial tissue is abundant and shows many fibroblasts. There is diffuse congestion and infiltration with leukocytes some of which occur in foci and include polymorphonuclear cells as well as lymphoid cells. Some eosinophil cells also occur. The walls of the vessels are thickened. Extravasations of blood are limited to the interstitial tissues. No red blood cells are present in the tubules.

Suprarenals: The medulla shows marked congestion and considerable diffuse hemorrhage. It also shows beginning postmortem autolysis. In the cortex the stroma is unusually abundant.

Thyroid: Most of the follicles are underdeveloped and contain none or very little colloid. The stroma is very cellular and abundant. It contains numerous leukocytes both of the mononuclear and the polymorphonuclear types.

Lymph Nodes: These show marked congestion; otherwise unnoteworthy.

Cerebral cortex: There is a diffuse extravasation of blood throughout the white matter.

Thymus: There is a marked increase in the stroma separating the parenchyma into unusually distinct lobules. This increase is, in part, due to proliferation of the connective tissue as indicated by numerous fibroblasts and,

Fig. 5.—Photomicrograph of lymph node embedded in the capsule of the thymus gland in Case 2, showing dilated lymph sinuses containing many large endothelial phagocytes (a) which have engulfed many red blood corpuscles.

in part, to the infiltration with blood. In some portions this hemorrhagic infiltration is so extensive that the lobules of thymus tissue appear as islands in a mass of blood cells. In some areas the stroma is infiltrated with a purulent exudate, in others it shows focal areas of necrosis. The larger vessels show a very thick wall due mostly to thickening of the adventitia. In several of them the lumen is almost completely occluded by cellular thrombi. In the perilobular tissue there are also foci of lymphoid and polymorphonuclear cells with begining necrosis suggesting miliary gumma.

The parenchyma shows marked congestion and diffuse hyperplasia of the reticular epithelial cells. In fact, so marked is this hyperplasia of these large pale cells that in many foci few lymphoid cells remain. There is also prolifera-

tion and swelling of the endothelial cells of the vessels. Hassall's bodies are numerous and show a tendency to cystic degeneration and dilatation. Often these cystic structures contain a purulent exudate. Some of the lobules are almost entirely destroyed by hemorrhage, only a narrow rim of the cortical substance persisting. The hemorrhages apparently occur first in the medullary substance which seems more readily broken down than the cortex. Throughout the lobules there is diffuse infiltration with leukocytes, including polymorphonuclear and eosinophil cells as well as lymphoid cells. Karyorrhexis of many of the nuclei occurs, in fact there are all stages between this diffuse leukocytic infiltration, necrosis and hemorrhage. In other words, the hemor-

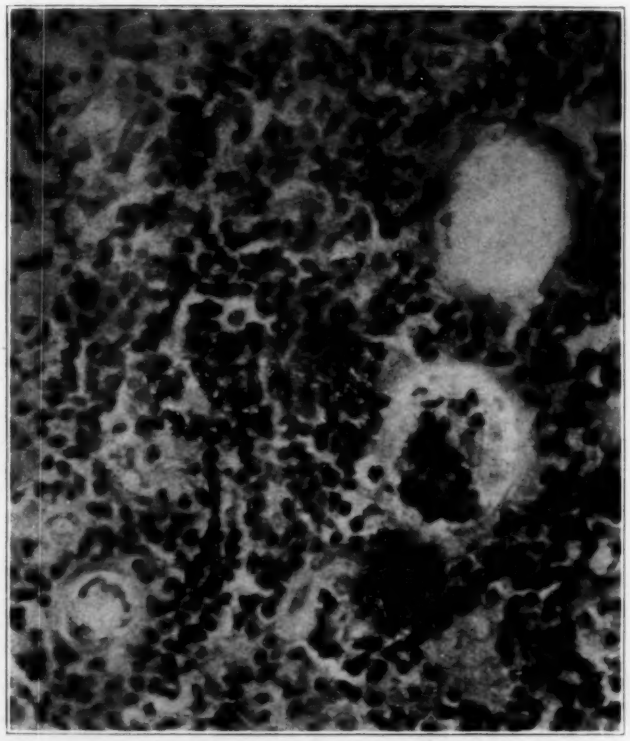

Fig. 6.—Photomicrograph of two dilated Hassall bodies in the thymus gland in Case 1. This area shows no hemorrhage but shows many scattered polymorphonuclear leukocytes and considerable proliferation of the epithelioid cells. Note the normal Hassall body in the lower left corner.

rhage is preceded by necrosis. Often the lobule has been almost replaced by blood, except a narrow rim of cortical tissue and a few Hassall's bodies embedded in the mass of red blood cells. Some of the smaller veins are distended with leukocytic thrombi.

Bacteriologic Examination.—Unfortunately no cultures were made at time of the necropsy. Bacterial stains of sections of the thymus showed occasional coccoid bodies but no definite organisms. No spirochetes were found.

Anatomic Diagnosis.—Cerebral hemorrhage; diffuse hemorrhagic infiltration of the thymus gland; multiple hemorrhages in the lungs, suprarenals, kidneys

and heart; subserous hemorrhages into the pleura, pericardium and capsule of liver; chronic interstitial pneumonia; parenchymatous degeneration of heart, liver, kidneys and pancreas; thrombosis of vessels of thymus, acute inflammation and focal necroses of the thymus gland.

CASE 2.—Baby P., white, male, aged 6 weeks, was admitted to the contagious hospital Jan. 1, 1921, with a provisional diagnosis of meningitis.

Family History.—The father was apparently in good health. Mother, aged 19 years, primipara, had a four plus Wassermann. Physicial examination of her heart gave findings suggestive of an aortitis.

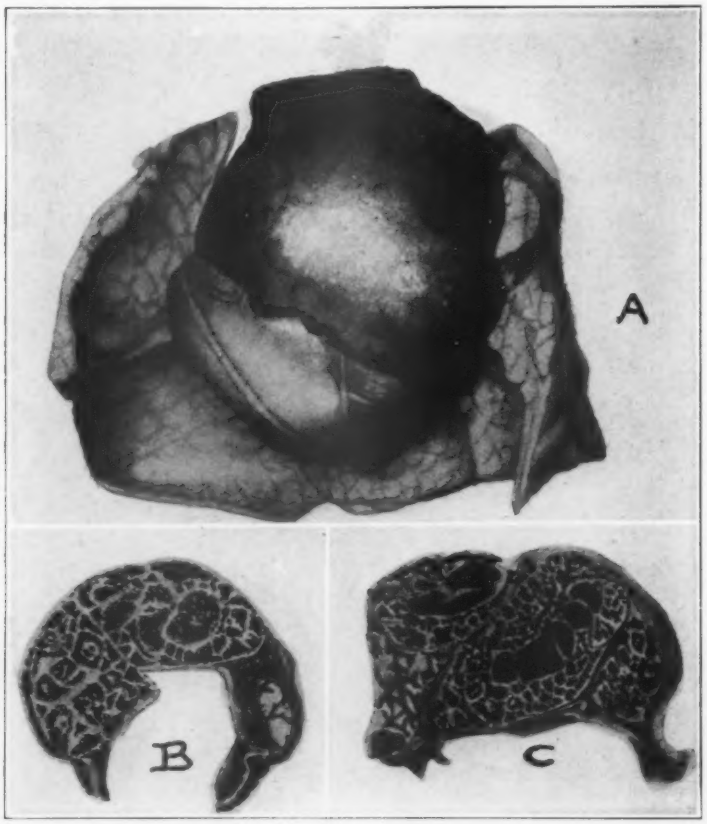

Fig. 7.—A. Drawing of the thymus in Case 2, showing its exact size and its relation to the heart and lungs.
B. Drawing of a cross section through the thymus gland of Case 1.
C. Drawing of a cross section through the thymus glands of Case 2.

Past History.—The baby was delivered by a dry labor which, however, was not unusually protracted, and was charted as a normal baby although the birth weight was only 5 pounds 8 ounces. The usual initial loss of weight brought the weight down to 4 pounds 9 ounces, and on the sixth day it was up to 5 pounds, remaining stationary the remainder of the stay in the hospital (ten days). From the third to the sixth day the temperature ranged from 103 to 106 F. Before and after this period it was normal. The temperature fell to

normal when diluted cow's milk was given with the breast feeding. At three weeks of age the patient was again examined and found to be a normal breast fed baby, except that it was fretful and colicky.

Present Illness.—One week before entering the hospital (5 weeks of age) the baby had a yellow color, had not gained weight and was in poor condition. It cried much, took the breast poorly and was very restless. Two days before admission there was some bleeding from the nose and mouth and the stools had become black. The night before entering the hospital the baby's condition became worse, showing a generalized spasticity and retraction of the head, and the eyes appeared to be set and glassy.

Physical Examination.—A fretful, desperately ill, undernourished baby, lying with its head drawn back, and at times giving a characteristic meningeal cry. There was marked jaundice. The extremities were spastic and the muscles of the neck tense. The anterior fontanel bulged markedly. The right eye showed a divergent strabismus. The left eye showed a ptosis of the lid. Both pupils were unequal and dilated. There was a slight horizontal nystagmus of both eyes. The heart was normal with no murmurs but with a very rapid rate. There was a slight umbilical hernia. The thumbs of both hands were flexed on the palms and the fingers were flexed over the thumbs.

Blood Wassermann was negative. It was noted that this blood did not clot, the red blood cells settling out at the bottom. A soft clot developed later. A lumbar puncture was made but the examination was unsatisfactory. The baby continued in a state of spasticity, with an occasional convulsion, and gradually became more feeble, dying twelve hours after admission.

Clinical Diagnosis.—Cerebral hemorrhage complicating hemorrhagic disease of the new-born.

NECROPSY REPORT

Macroscopic Examination.—Unfortunately, complete necropsy data on this case are not available. Through the kindness of Dr. W. S. Campbell we received the brain, kidneys, spleen and all of the thoracic organs for study. The heart was normal. The kidneys showed marked fetal lobulation, otherwise appeared to be normal. The spleen was normal, except for marked congestion. The lungs showed a distinct lobulation with areas of dark gray partly consolidated tissue. These areas on section had an edematous transluscent appearance. Most of the lung tissue was air containing. There was a denser framework than is normal. There was also considerable hemorrhage in the hilum of the lungs, extending, on the one hand, into the lung tissue along the bronchi and, on the other hand, continuous with a large hemorrhagic mass situated in the upper anterior mediastinum. This mass is composed of an enlarged thymus markedly infiltrated with blood, extending from the hilum of one lung to that of the other and covering the greater part of the pericardium. Its outer surface is smooth and reddened but there is no free blood. This enlarged thymus weighs 28.4 gm. and measures 5 x 4.2 x 2.4 cm. It is very firm in consistency. It cuts with resistance and the cut surface has a dark red color with an interlacing network of grayish white markings giving the hemorrhagic tissue a lobulated appearance. In other areas there are islands of pale yellow tissue embedded in a hemorrhagic matrix. While the blood is diffused throughout the gland, near the center there were several clots of blood from 6 to 8 mm. in diameter. The right lobe of the thymus shows more extensive infiltration with blood than the left, and is accordingly very much larger. The capsule of the gland is infiltrated with blood. No hemorrhages were found in the other viscera. There was a thin layer of blood beneath the pia on the lateral surfaces and base of the brain but no hemorrhage in the cerebral cortex. The ventricles contained no blood.

Microscopic Examination.—Heart: Many of the muscle fibers contain vacuoles often associated with obliteration of the cross striations and even distintegration of the cytoplasm. The connective tissue is increased and contains many leukocytes, most of which appear as small dark staining round cells occasionally arranged in small foci. In the latter a few polymorphonuclear leukocytes may be seen.

Lungs: The pleura is thick. The alveolar walls are thickened, cellular and contain many leukocytes, polymorphonuclear as well as mononuclear, the latter being most abundant. The walls of the vessels, especially the adventitia, are thickened, and in some the lumen is reduced in size. Some of the bronchi are filled with a purulent exudate; others appear to be normal. The peribronchial connective tissue is unusually abundant, and in some areas it is infiltrated with blood. There is also considerable infiltration with lymphoid cells. In addition, near the hilum, there is considerable embryonic fat and clusters of large round cells resembling endothelial phagocytes containing brown pigment granules. The alveoli vary in appearance. Some are empty, others are filled with desquamated, round, alveolar epithelial cells and serum. Others contain a purulent exudate. Many show a swollen culoidal epithelial lining. In some of the bronchi there is a fibrinous exudate containing scattered red blood cells.

Spleen: There is marked congestion; otherwise the organ is normal.

Kidney: The glomeruli are numerous and the cells are swollen. Few red blood cells are seen in the capillary tufts. The tubular epithelial cells are swollen and some are disintegrated. A few of the cells are calcified. There is some fibrosis and lymphoid infiltration throughout the organ.

Aorta: There is swelling and edema of the elastic fibers of the media and infiltration of lymphoid cells especially about the vasavasorum.

Lymph nodes: The bronchial nodes are intensely congested, the sinusoids are distended and contain many large endothelial phagocytes, many of which are filled with red blood cells. There is marked swelling and proliferation of endothelial cells. Some of the larger nodes about the trachea show much the same picture. In one node the endothelial proliferation is so extensive about the periphery as to resemble a collar of tumor tissue. Besides the congestion there is also some slight diffuse hemorrhage, especially in foci containing pus cells and in which beginning necrosis is evident. The marked endothelial proliferation is associated with atrophy of the lymphoid elements.

Thymus: The architecture of the gland is exaggerated by the marked thickening of the perilobular fibrous tissue. The increase of these septa is due to extensive diffuse hemorrhage and suppuration. Foci of necrosis are present but poorly outlined. The capsule is also markedly thickened for the same reason and shows many fibroblasts and new formed capillaries, especially extending where the blood is most abundant. Some of the broad interlobular septa contain no hemorrhage but show extensive purulent exudation and occassionally poorly outlined areas of necrosis. Leukocytes of various types including polymorphonuclears and eosinophils abound in the stroma. Several small hyperplastic lymph nodes are adherent to the capsule of the thymus. In the stroma there is also swelling of the endothelial cells of the vessels and marked accumulation of lyphoid cells about these vessels. This perivascular reaction is very striking in some areas. The thymus lobules appear as islands of cellular tissue in the hemorhagic tissue. Hassall's corpuscles are numerous. There is marked congestion and hyperplasia of the reticular epithelial cells. The latter are so numerous that in some lobules few of the smaller thymic elements are left. There are numerous eosinophil cells. In many lobules there are scattered foci of lymphoid and polymorphonuclear cells showing beginning necrosis. Occasionally, small hemorrhages may be seen in these foci. In fact, there are all stages between the acute inflammatory reaction, necrosis of the center of the lobule and its almost complete replacement by hemorrhage. In some lobules the hemorrhage has destroyed the greater part so that only a narrow rim of the cortex still persists. Even in these areas the Hassall's bodies may still persist. Many of the small veins are filled with pus cells.

Bacteriologic Examination.—Negative, as in Case 1.

Anatomic Diagnosis.—Bronchopneumonia, chronic interstitial pneumonia; thymus apoplexy; subpial hemorrhage of brain; acute inflammation and focal necroses of the thymus; thrombophlebitis of veins of thymus, parenchymatous degeneration of the heart and kidneys.

DISCUSSION

The two cases are similar in many respects. Symptoms of meningeal irritation, lateral nystagmus and generalized icterus were present in both infants. Labor, while not normal, was not unduly difficult or prolonged in either case. In both cases there was a marked increase in the coagulation time of the blood. In each case the necropsy showed a cerebral hemorrhage, inflammatory changes in the lungs suggestive of syphilis and a diffuse hemorrhagic infiltration of the thymus in which the extravasation of blood was both intralobular and interlobular and was associated with suppuration, necrosis and marked proliferation of the reticular epithelial cells. The cases differ in that the second patient was much older than the first. The hemorrhages were more generalized and extensive in Case 1. Labor was more difficult in Case 1. The immediate cause of death in Case 1 was cerebral hemorrhage, while in Case 2 the bronchopneumonia was probably the more immediate factor causing death. There was considerable organization of the hemorrhage in Case 2, indicating an older process than in Case 1 in which no new capillaries or fibroblast were found. In both cases the Hassall's corpuscles were numerous but in Case 1 they were dilated and often contained a purulent exudate forming early DuBois abscesses.[15] On the other hand, Case 2 showed a striking perivascular inflammatory reaction with swelling of the vascular endothelium and also marked thrombophlebitis of the smaller veins. One of the large veins in Case 1 was partly occluded by a thrombus (Fig. 2).

The relation of these cases to syphilis is of considerable interest. Case 1 presented no positive clinical findings. The Wassermann test on the bloods of both the father and infant were negative. No examination of the mother's blood could be obtained. Several members of the family showed evidences of constitutional weakness and syphilis could not be excluded even with negative blood findings. The clinical findings in Case 2 were more suggestive of syphilis. The Wassermann reaction on the blood of the mother was strongly positive but in the case of the child it was negative. There was no opportunity to repeat this test and a single negative reaction is not conclusive. The anatomic changes in both cases, while not pathognomonic, afford strong presumptive evidence of syphilis. Examination of the tissues for spirochetes in both cases was negative but this was most likely due to improper fixation. The interstitial inflammatory changes in both lungs suggest syphilis. The lobules of the thymus gland that are not disintegrated by hemorrhage show changes in both cases that are regarded as characteristic of congenital syphilis. In both cases there was marked

15. Oliver, J.: Syphilitic Disease of the Thymus in Infants and the Mode of Origin of the DuBois Abscesses, Am. J. Dis. Child. **13**:158 (Feb.) 1917.

proliferation of the reticular epithelial cells associated with more or less atrophy of the thymic lymphocytes, a change that Simmonds,[16] Hart,[2] Hecker,[17] Schlesinger, Dudgeon [18] and Klose [12] note as a characteristic change in the thymus of congenital syphilis. Furthermore, the early stages in the formation of DuBois abscess as described by Oliver [15] were present in Case 1. While Case 2 does not show this dilatation of the Hassall bodies with the beginning formation of DuBois abscesses (which are said to be present only in fetal syphilis), it does show a very marked perivascular lymphoid infiltration and hyperplasia of the vascular endothelium.

There is considerable difference of opinion regarding the relation of these extensive hemorrhages in the thymus and syphilis. Mendelsohn [10] and Schlesinger [9] maintain that there is an etiologic relation between thymus apoplexy and syphilis. Hart [2] and Dudgeon [18] deny that such relationship exists, while Hecker [17] and Simmonds [16] omit any reference to thymus hemorrhages in describing the histologic changes in the thymus in congenital syphilis. On the other hand, it is significant that in all the reported cases in which a detailed microscopic description is available (five cases) there was either a family history or anatomic changes that were either strongly suggestive or positively indicative of syphilis. In the other cases there were some with a specific history and others with nothing to suggest syphilis. Our cases undoubtedly have a syphilitic basis, yet we are unwilling to give the impression that extensive hemorrhages in the thymus are necessarily pathognomonic of syphilis.

The etiology of thymus apoplexy is obscure. So few cases have been reported and such varying causes have been ascribed that final judgment must wait on a larger number of thoroughly described cases. It is probable that one or more of four factors play a part in each case. Circulatory stasis as a cause, especially in a thymus the seat of marked hyperplasia is emphasized by Hart,[2] Klose [12] and Marfan.[5] When this is the main factor, the hemorrhage is diffused throughout the gland giving the appearance of a hemorrhagic infarct. A second factor is trauma, especially birth trauma, which is stressed by Weber, Friedleben, Raudnitz and Klose. The last author quotes Penkert and Veit as suggesting that thymus apoplexy is not an uncommon cause of death of new-born infants. A third factor is the presence of a hemor-

16. Simmonds, M.: Die Thymus bei Kongenitaler Syphilis, Virchows Arch. f. path. Anat. **194**: (Suppl.) 213, 1908.

17. Hecker, R.: Beiträge zur Histologie und Pathologie der congenitalen Syphilis sowie zur normalen Anatomie des Fetus und Neugeborenen, Deutsch. Arch. f. klin. Med. **61**:1, 1893.

18. Dudgeon, L. S.: A Contribution to the Pathology of the Thymus Gland, J. Path. & Bacteriol. **10**:173, 1905.

rhagic disease of the new-born, that is, a defect in the coagulating mechanism of the blood such as occurred in both of our cases especially in the first one. This hemorrhagic tendency is frequently associated with if not due to, some underlying infectious process analogous to hemorrhages in the medulla of the suprarenal so commonly found in the new-born.[19] The fourth and probably the most important factor is the rôle played by infectious diseases, especially syphilis. It is very common to find small petechial hemorrhages in the thymus in infectious disease, in fact, Dudgeon noted them in 95 per cent. of the cases of pneumonia in infants. These minor hemorrhages are not to be confused with the more extensive blood extravasations referred to as thymus apoplexy in which the rôle of infection is not so clear. Undoubtedly, the hyperemia associated with an infection predisposes to hemorrhage. The fact that necrosis and suppuration preceded the hemorrhage in both of our cases makes the presence of an infection, probably syphilitic, most likely. Here, again, the same factor of infection plays the important rôle in hemorrhage in the suprarenal of the new-born.[19]

Another point of interest is that the early history of bleeding from the nose and mouth occurring in each of our cases indicated a hemorrhagic tendency and should have suggested appropriate serum or whole blood therapy to offset any complications, although with a syphilitic background, as in our cases, the results would have been the same.

The symptoms in our cases suggested a tendency to general hemorrhages, but there was nothing to indicate that the hemorrhage had involved the thymus gland. Nor have we found anything in the literature which would aid in the diagnosis of a thymus hemorrhage.

The possibility that the rapid enlargement of the thymus gland from the diffuse infiltration of blood could have been the immediate cause of death in a mechanical way cannot be excluded, especially in Case 2. The mechanical action of an enlarged thymus unassociated with other factors has been exaggerated and we do not feel that the evidence available justifies it as the cause of death in thymus apoplexy.

SUMMARY

Thymus apoplexy is a rare condition of extensive hemorrhage throughout the gland and is not to be confused with the smaller petechial hemorrhages frequently occurring in acute infections.

It usually occurs in very young infants or the new-born and is often associated with sudden death.

It seems to be associated with syphilis more than any other factor, but circulatory stasis, trauma, nonspecific infections and a hemorrhagic tendency are contributing, if not the main, factors in some cases.

There is no way of making a clinical diagnosis.

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19. Litzenberg, J. C., and White, S. M.: Hemorrhage in the Adrenal Glands of Infants, J. A. M. A. **51**:1964 (Dec. 5) 1908.

THE FOOD REQUIREMENTS OF CHILDREN

IV. CARBOHYDRATE REQUIREMENT

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The carbohydrate in the diet of the growing child has, as far as is known, no specific function to perform. Nevertheless, it is a very essential component of the diet. It serves mainly as a source of energy, supplying the necessary calories which are not furnished by fat and protein. In so doing, however, carbohydrate accomplishes other purposes. It is the most efficient sparer of protein, being for this purpose superior to fat. This function of carbohydrate is so well known and has been so frequently discussed in the literature that it need not be taken up in detail here. It has been accepted generally that carbohydrate is essential for complete metabolism of fat, and that in the absence of carbohydrate from the diet, or when the amount is very low, fat is incompletely burned and acidosis may result.

When digestion is normal, a reasonable intake of carbohydrate is almost, if not quite, completely utilized in the body, leaving no residue to be eliminated in stools and urine. The excess that is not immediately used for energy is stored in the form of glycogen to be used later for energy or is converted into fat and added as such to the tissues of the body.

Carbohydrate is the most economical food from a physiologic as well as a commercial point of view. Physiologically, it is economical because of its complete utilization and because the energy required for digestion, that is, the "cost of digestion," is much lower than that of fat or protein. The commercial economy in carbohydrate foods is well known. They can be produced more cheaply than other foods; they can be stored for a long period without significant deterioration; they can be shipped and marketed in a compact form and are not readily affected by changes of temperature or by exposure. Because of these facts the market price of carbohydrate foods is much lower than that of the foods which are composed mainly of fat and protein. Table 1 gives the number of calories of carbohydrate which could be purchased for 10 cents at a small retail store in New York City, Feb. 1, 1922. For comparison are given the number of calories in fat and protein foods which could be purchased for the same amount at the same time and place.

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* Received for publication, March 17, 1922.

* From the laboratories of the Rockefeller Institute for Medical Research and the Babies' Hospital.

Carbohydrates form the greatest part of the diet of the human race at every period of life. The nursing infant receives a high proportion of carbohydrate as lactose in woman's milk, nearly one-half of the caloric value of the milk being due to the sugar. The nursing infant takes about 50 gm. lactose daily at the end of the first month and an average of 80 gm. daily during the latter part of the nursing period. Infants taking modifications of cow's milk usually receive more carbohydrate than do nursing infants. This is given because the amount of fat in modifications of cow's milk is in most cases considerably lower than that in woman's milk. Although a higher proportion of protein is given, this does not entirely make up for the reduction in the calories furnished as fat and consequently a larger amount of carbohydrate must be supplied.

TABLE 1.—CALORIES PURCHASABLE FOR TEN CENTS. FEB. 1, 1922

Articles	Retail Price	Number of Calories
Carbohydrate Foods:		
Sugar, granulated	6 cents per pound	3,100
Karo corn syrup	20 cents per 2.5 pound can	1,970
Oatmeal	12 cents per 20 ounce package	1,930
Rice	12 cents per pound	1,360
Bread	9 cents per 15 ounce loaf	1,270
Cream of wheat	30 cents per 28 ounce package	980
Potato	5 cents per pound	770
Jam	30 cents per pound jar	530
Fat Foods:		
Butter	49 cents per pound	740
Olive oil	65 cents per pint	600
Cream, Sheffield X (includes some protein and sugar)	32 cents per half pint	240
Protein Foods (include some fat):		
Cheese, American	35 cents per pound	590
Lean beef, round	44 cents per pound	200
Eggs, fresh brown	60 cents per dozen	180
Mixed Food:		
Milk, Sheffield, Grade A	18 cents per quart	355

The nursing infant receives carbohydrate entirely in the form of lactose. The infant on modifications of cow's milk may take lactose entirely or part lactose and part saccharose, maltose, dextrin, or starch, or a combination of these. It is not usual for any large proportion of the carbohydrate to be given as starch during the first year. When a mixed diet is taken at least one-half of the carbohydrate is usually in the form of starch, the rest being sugars—lactose, saccharose and fructose with occasionally a certain amount of dextrin and maltose.

The amount of carbohydrate taken by children more than 1 year of age varies according to the theories of the physician and the notions of the parent and even more according to the habits and tastes of the child. The carbohydrate variation is greater than that of any other constituent of the diet. Some children habitually take large amounts of bread, others live mainly on cereals, while with still others potatoes form the predominant article of diet. Many children consume an excessive amount of sugar, taking several teaspoonfuls on cereal and in

other foods and sometimes even having sugar added to the milk taken. The relative amount of sugar taken by these children is steadily increased with age, since the child's palate demands a marked degree of sweetness in all foods and will not take those which do not taste sweet. In such cases the amount of sugar consumed soon forms a surprisingly large proportion of the diet to the exclusion of the other needed constituents.

Many children take, besides the amount of granulated sugar eaten with foods, a great deal in the form of jam, marmalade, jelly or syrup. It is often forgotten that syrup and honey are practically pure carbohydrate in a concentrated form, and that jam, marmalade and jelly usually contain from 80 to 90 per cent. sugar. Many a mother or physician who would think an ounce of granulated sugar excessive does not realize that an ounce of syrup or a rounded tablespoonful of jam contains practically the same amount of sugar. To these sources of carbohydrate must be added candy. There are few children who get no candy and the majority take several pieces and not a few as much as half a pound daily. A small piece of candy is equivalent to about one teaspoonful of sugar. It is obvious that a few pieces of candy increase the carbohydrate intake appreciably.

The degree to which sugar has come to form a prominent part of the diet of the American people is a cause for serious reflection. One hundred years ago the consumption of granulated sugar averaged only 8 pounds per capita. Last year the average was 84 pounds. The amount consumed as candy is a very large item in sugar consumption. The statement was made a few years ago by an official of a corporation operating 5 and 10 cent stores that their annual sales of candy exceeded 60,000 tons.

The carbohydrate intake of more than a hundred healthy children specially studied by us is shown in Charts 1 and 2. In Chart 1 are given the values in grams of the total carbohydrate taken daily. The curves shown are those representing the grams of carbohydrate which would be required to supply 50 per cent. of the total calories which are needed, according to our estimates,[1] at the different ages. Our investigations have shown that this proportion of the total calories, that is, 50 per cent., is the average taken as carbohydrate by a normal healthy child. The figures on which this average is based will be presented later.

In Chart 2 are given the values for the carbohydrate intake in grams per kilogram of body weight. The curves represent the grams of carbohydrate supplying 50 per cent. of the caloric requirement per kilo.

Charts 1 and 2 illustrate the wide variation in the carbohydrate intake of healthy children. This is most evident in the chart showing grams per kilogram. There are more very high values than very low

1. Holt, L. E., and Fales, H. L.: Am. J. Dis. Child. **21**:1 (Jan.) 1921.

ones and several instances of an intake of more than 15 gm. carbohydrate per kilogram. Chart 1 shows that there was more consistency in the total amount of carbohydrate taken daily. There are few low values, but several exceedingly high ones. One girl, 8 years of age,

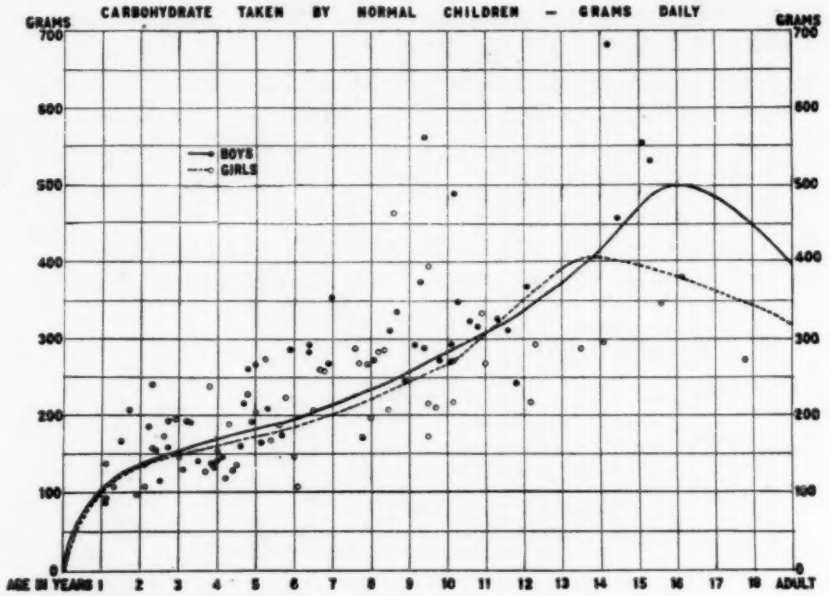

Chart 1

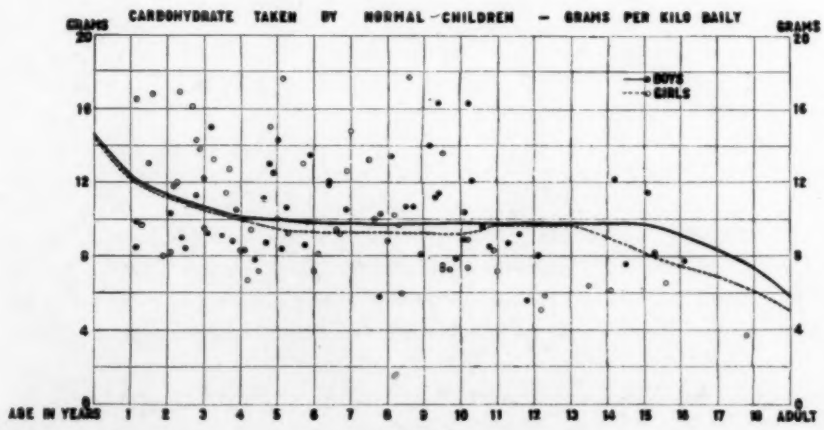

Chart 2

took 464 gm. carbohydrate daily. One boy, 9 years of age, took 560 gm.; another, aged 10, took 488 gm. and one, aged 14, took 683 gm. daily.

The average intake according to years is shown in Table 2, which gives the values for boys and girls separately and for both sexes grouped

together. It will be seen that the total daily intake increases with fair regularity with the years, while the intake per kilogram decreases with the years. The average of all the cases, regardless of age, is about 10 gm. per kilogram. It is interesting to note that the carbohydrate intake per kilogram of the boys aged 14 to 16 showed a marked increase over that of the boys a little younger.

The observations reported in the literature, in which the carbohydrate intake of children after infancy was ascertained, show variations quite as wide as those in our own cases. As a rule, the amount of carbohydrate per kilogram of body weight taken by young children was higher than that taken by older children. The children studied by Müller [2] had very high intakes of carbohydrate, nearly all over 10 gm. per kilogram, while several children took as much as 17 gm. The intake of carbohydrate in Camerer's cases was low, as were the other

TABLE 2.—AVERAGE CARBOHYDRATE INTAKE OF CHILDREN. ORIGINAL OBSERVATIONS

Age, Years	Boys			Girls			Both Sexes		
	No. of Cases	C-H Intake		No. of Cases	C-H Intake		No. of Cases	C-H Intake	
		Total Gm. Daily	Gm. per Kg.		Total Gm. Daily	Gm. per Kg.		Total Gm. Daily	Gm. per Kg.
1–2	2	90	9.2	5	154	12.8	7	128	11.8
2–3	4	142	10.0	7	179	13.3	11	165	12.1
3–4	6	147	10.9	4	176	11.7	10	158	11.2
4–5	7	178	10.2	5	166	9.4	12	173	9.8
5–6	5	219	11.1	5	211	11.9	10	215	11.5
6–7	3	280	11.5	5	196	9.3	8	228	10.1
7–8	2	261	10.3	3	274	11.2	5	269	10.8
8–9	4	291	10.8	5	288	10.5	9	289	10.6
9–10	5	357	12.2	4	247	8.9	9	308	10.7
10–11	6	338	10.9	3	272	8.5	9	317	10.2
11–12	3	292	7.8	1	268	7.2	4	286	7.7
12–13	1	366	8.0	2	257	5.5	3	293	6.3
13–14	..	....	....	1	287	6.4	1	287	6.4
14–15	2	571	9.9	1	296	6.2	3	480	8.9
15–16	2	541	9.6	1	346	6.6	3	476	8.1
16–17	1	380	7.8	..	....	....	1	380	7.8
17–18	..	..	....	1	272	4.8	1	272	4.8

constituents. Gephart [3] found that the amount of carbohydrate taken by the boys of St. Paul's School was much in excess of the average adult consumption, averaging more than 600 gm. daily. This represents an average of 13.7 gm. per kilogram for the youngest group of boys who averaged 13 years of age, 12.4 gm. per kilo for the group of boys who averaged 14½ years and 9.9 gm. for those averaging 16 years.

The amount of carbohydrate in the usual adult dietary is from 400 to 550 gm. daily, which represents from 5 to 8 gm. per kilogram of body weight.

2. Müller, E.: Biochem. Ztschr. **5**:143, 1907.
3. Gephart, F. C.: Boston M. & S. J. **176**:17, 1917.

Murlin[4] found that the men in the United States Army training camps took on the average 545 gm. carbohydrate daily. This is equivalent to 8.2 gm. per kilogram, the average weight being 146 pounds, or 66.5 kilograms.

From the data obtained concerning the diet taken by the normal children studied by us it was possible to calculate approximately the amounts of carbohydrate taken as sugar and as starch by these children. The values obtained are only approximate, since the relative amounts of sugar and starch used in cooking the various articles, such as cake, pudding, etc., could, in most cases, be only estimated from a knowledge of common recipés. It may be assumed, however, that our estimates are reasonably accurate.

It is surprising that the average of all the cases, regardless of age, showed that 51 per cent. of the carbohydrate intake was in some form of sugar. The proportion of sugar ranged from 27 to 82 per cent., but more than two-thirds of the values were between 40 and 60 per

TABLE 3.—AVERAGE AMOUNTS OF STARCH AND SUGAR TAKEN

Age in Years	No. of Cases	Gm. Carbohydrate as		Age in Years	No. of Cases	Gm. Carbohydrate as	
		Starch	Sugar			Starch	Sugar
1–2	7	65	63	10–11	9	161	156
2–3	11	71	94	11–12	4	136	150
3–4	10	85	73	12–13	3	162	131
4–5	12	86	87	13–14	1	133	154
5–6	10	101	114	14–15	3	277	203
6–7	8	111	117	15–16	3	229	247
7–8	5	137	132	16–17	1	216	164
8–9	9	128	161	17–18	1	108	164
9–10	9	149	159				

cent. In Chart 3 are given the proportions of starch and sugar taken by each child, arranged according to age. This shows that there is comparatively little individual variation in the distribution of the carbohydrate intake as starch and sugar. It is apparently usual in the mixed diet of children to give practically equal amounts of starch and sugar. It should be noted that the value for sugar includes not only the saccharose used in cooking or on cereals, etc., but also the fruit sugars and the lactose of the milk which was taken separately or which was used in the preparation of other foods.

Table 3 gives the average values according to years for the daily intake of starch and sugar.

It was also possible to estimate roughly the proportion of different sugars which made up the sugar intake. Some interesting observations were thus brought out. Table 4 shows the averages, according to years, of the grams of lactose, saccharose and fruit sugars taken by the children studied. It will be seen that the lactose intake does not vary

4. Murlin, J. R., and Hildebrandt, F. M.: Am. J. Physiol. **49**:531, 1919.

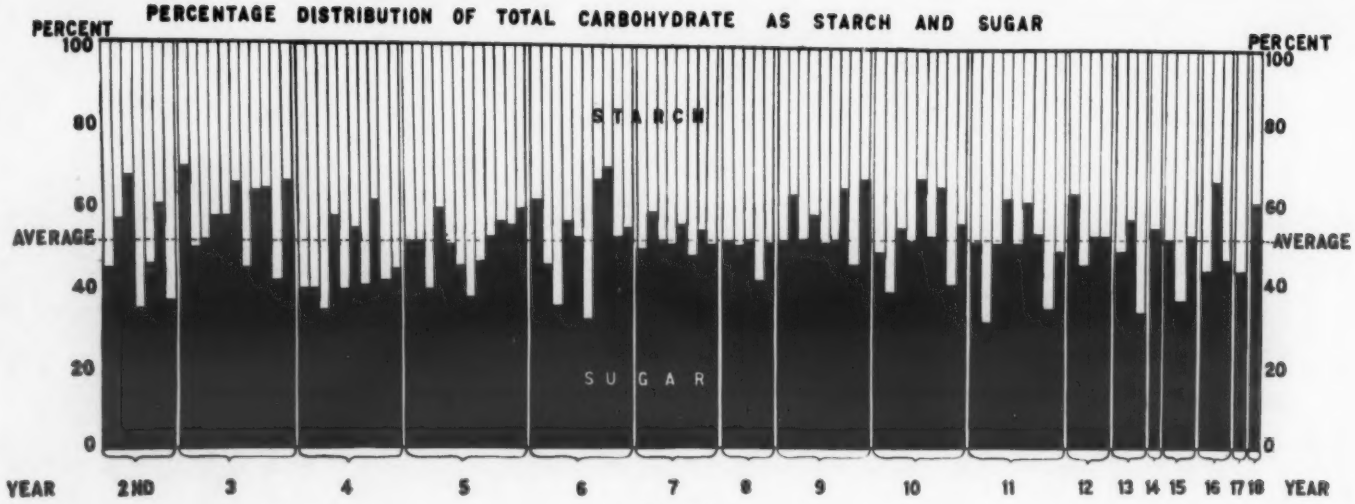

Chart 3

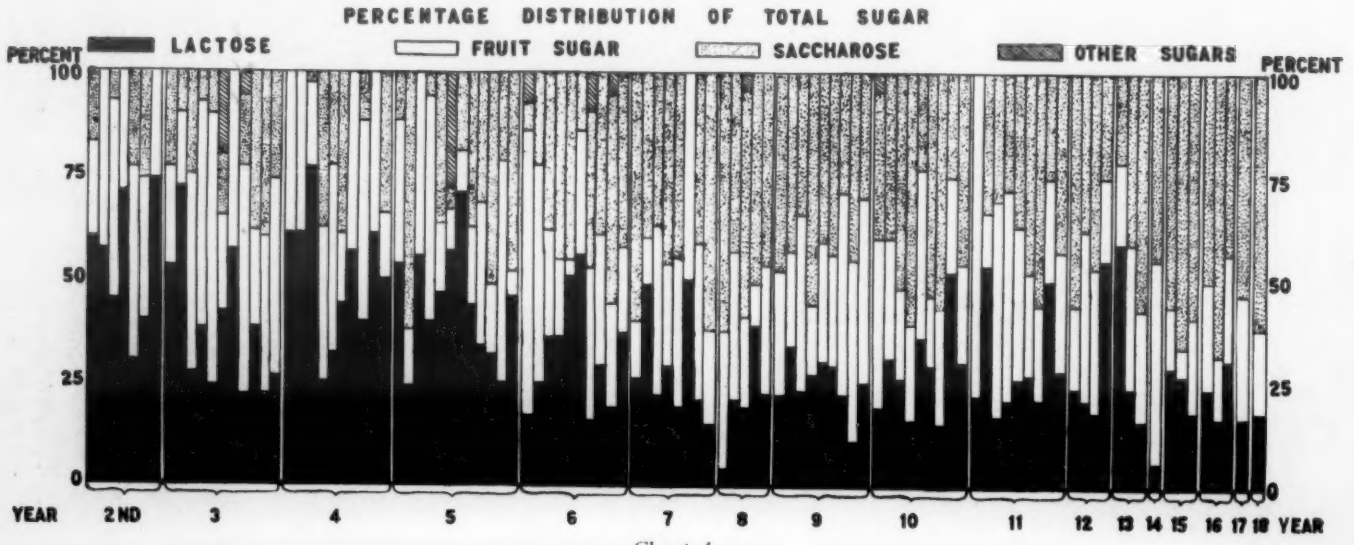

Chart 4

widely. The saccharose taken, however, shows an almost steady increase with age up to the eleventh year, with a marked increase during adolescence, the amount taken at that time being about ten times as much as the average taken by children under 4 years. It is surprising to note how much of the sugar was supplied by fruits. This value includes all the carbohydrate in the fruit. This is largely fructose but some of it is saccharose, and there is included in some instances a small amount of starch, for example, in apples and bananas when not thoroughly ripe.

In Chart 4 are shown the percentages of the total carbohydrate taken as different sugars by each child, the values being arranged according to age.

TABLE 4.—AVERAGE AMOUNTS OF DIFFERENT SUGARS TAKEN

Both Sexes.—Average Gm. Daily

Age, Years	No. of Cases	Lactose	Saccharose	Fruit Sugars*	Other Sugars	Total Sugars
1-2	7	30	9	24	..	63
2-3	11	33	19	40	2†	94
3-4	10	34	12	27	..	73
4-5	12	36	26	24	1‡	87
5-6	10	35	39	37	3§	114
6-7	8	29	55	33	..	117
7-8	5	24	69	38	1†	132
8-9	9	40	64	57	..	161
9-10	9	39	76	43	1†	159
10-11	9	44	53	59	..	156
11-12	4	42	59	44	5‡	150
12-13	3	48	48	35	..	131
13-14	1	9	69	76	..	154
14-15	3	48	124	31	..	203
15-16	3	55	140	52	..	247
16-17	1	27	87	50	..	164
17-18	1	29	102	33	..	164

* This includes all sugars occurring in fruit taken; largely fructose, but includes considerable saccharose and occasionally very small amounts of starch.
† Honey (levulose and dextrose).
‡ Maltose.
§ Honey and maltose.

The economic advantage of carbohydrate foods over fats and proteins has brought about a tendency to allow carbohydrate to form an excessive proportion of the modern diet. There are several important disadvantages in this procedure. The production of diabetes must be reckoned as a possible danger, as has recently been suggested.[5] If the proper caloric intake is maintained, a very high proportion of carbohydrate necessitates a low proportion of either fat or protein. Hence, there is a possible danger of reducing the amount of fat or protein below that which is necessary for normal nutrition. When a diet high in carbohydrate and low in fat and protein is taken, there may result an excessive retention of water in the tissues of the body. High carbohydrate feeding leads also to an excessive deposition of fat in the body. This condition is often seen in infants fed on sweetened condensed

5. Micheal, J. C.: Arch. Dermat. & Syph. **2**:455 (Oct.) 1920.

milk or on the proprietary foods, which are chiefly carbohydrate. It is quite usual with such feeding to achieve a rapid gain in weight. Infants fed in this way, however, are usually found to have very low resistance to infection. Their tissues are high in fat and water but low in muscle. When a digestive disturbance occurs, or when an infection takes place, this unnatural weight is rapidly lost and the child often succumbs readily. A similar condition was produced experimentally in pigs by Washburn and Jones.[6] They found that young pigs fed on sweetened condensed milk put on an excessive amount of fat. The protein increase in their bodies was, however, much below normal, and the bone development was defective, the bones being only two-thirds as strong as when whole milk was fed. Table 5 gives a summary of some of their findings.

There is a growing belief that the large and constantly increasing proportion of carbohydrate in the diet of civilized races has a very important relation to the prevalence of dental caries. It has been

TABLE 5.—COMPARISON OF GROWTH IN SEVEN WEEKS OF SIX PIGS ON CONDENSED MILK WITH SIX PIGS ON WHOLE MILK

Feeding	Calorie Intake Daily	Weight, Gain in Kg.	Fat, per Cent. of Gain	Protein, per Cent. of Gain	Breaking Strength of Femur in Pounds
Whole milk	1,370	11.35	9.2	15.61	362
Sweetened condensed milk	1,270	8.10	23.65	10.92	243

Whole milk contained fat, 3.3; sugar, 5.2; protein, 3.6 per cent.
Sweetened condensed milk contained fat, 1.6; sugar, 9.8; protein, 1.6 per cent.

observed that Arctic peoples, whose diet is almost entirely fat and protein with but very little carbohydrate—and that usually in the form of starch, rarely suffer from dental caries.

Stefansson, the Arctic explorer, has stated that he himself has examined 500 skulls which were dug up from an old cemetery in Iceland of about the eleventh century. In only one skull was an imperfect tooth found and that was evidently the result of injury. He further stated that the Eskimos who live on a meat diet have perfect teeth, but, when they come in contact with civilization and eat the foods of other races they suffer severely from dental caries.

Furthermore, archeologic researches have shown that dental caries was prevalent in ancient Egypt. More recently the discovery of a very primitive human skull in Rhodesia has shown that dental caries existed in earliest times. Both of these localities are tropical or subtropical in climate and the early diet was probably composed largely of plant foods and hence was predominantly a carbohydrate diet, a complete contrast to that taken by the Arctic peoples.

6. Washburn, R. M., and Jones, C. H.: Vermont Agric. Exper. Sta. Bull. 195.

Whether the tendency to dental caries is due to an excess of carbohydrate or to a consequent reduction of other constituents of the diet—fat, protein, mineral salts or vitamins—has not yet been established.

Of great importance, also, is the effect on digestion of a diet in which the proportion of carbohydrate is excessive. When a very large amount of carbohydrate, especially in the form of sugar, is taken into the digestive tract at one time, it is often impossible for absorption to take care of it. The consequence of this is excessive fermentation in the intestine, due to bacterial action, with the formation of carbon dioxid and organic acids, which may be very irritating to the mucous membrane of the intestine. This excess of acid usually causes a quickened peristalsis with large, loose, acid stools. The result is a decreased absorption of all the food constituents and frequently a serious diarrhea. When the diet contains an excess of carbohydrate in the form of starch, somewhat different symptoms frequently develop. There is often constipation, great abdominal distention, flatulence and colic.

TABLE 6.—GRAMS OF CARBOHYDRATE COMBINED WITH ONE GRAM VEGETABLE PROTEIN

Food	Gm. Carbohydrate per Gm. Protein	Food	Gm. Carbohydrate per Gm. Protein
Peanut butter	0.6	Bread	5.8
Soy beans	0.6	Rice	6.4
Walnuts	0.7	Cream of wheat	6.9
Peas	2.4	Potatoes	8.4
Lima beans	3.7	Carrots	8.4
Oatmeal	4.2		

Usually these disorders of digestion are acute and not very severe, yielding quickly to proper dietetic treatment. When, however, they are frequently repeated or are prolonged through lack of proper dietary adjustment, they lead to serious chronic disturbances with marked loss in weight. This condition is often difficult to control and a very great reduction in the carbohydrate of the diet is required for a long time before the normal tolerance for carbohydrate is reestablished. This condition is most frequently seen in the second and third years of life.

In the discussion of the protein requirement of the child we have stated that if vegetable proteins are depended on to supply the protein need during growth very large amounts of carbohydrate are inevitably given, since vegetable proteins occur only in combination with large amounts of starch. Table 6 shows the amount of carbohydrate, usually in the form of starch, which is combined and necessarily given with each gram of vegetable protein in some common foods. It will be seen from this table that nuts and soy beans are the only foods which supply much vegetable protein without including very large amounts of carbohydrate.

Although nuts have been found to be well utilized by adults without disturbance of digestion, the wisdom of giving them to children in any considerable quantity is questionable. It is not advisable to depend on them as a source of protein. It would appear from its chemical composition that the soy bean is an excellent source of vegetable protein. This vegetable, used so extensively in China, is not familiar to the American people. It has a peculiar flavor, not very palatable according to our tastes, and on that account will probably not gain any great popularity in this country, where other sources of protein are readily available.

In the other articles of food which supply vegetable protein there is so much carbohydrate combined with the protein that there is danger of serious disturbance of digestion from the excess of carbohydrate. It is evident that for this reason alone, as well as for the others given in a preceding article, it is not wise to depend on vegetable foods to supply the protein need of the child.

As has already been stated, in addition to the positive harm which may follow excessive use of carbohydrate in the diet of the child, there must always be considered the additional disadvantage which follows this plan of feeding because of the inevitable reduction of fat and protein.

It has been shown that a definite amount of protein should be included in the diet of the growing child.[7] It seems rational to allow in the diet at least as much fat as protein.[8] The total calories needed at any age can be estimated with a fair degree of accuracy.[1] Hence, the amount of carbohydrate required is determined by subtracting from the total caloric need the calories supplied by the needed amounts of fat and protein. On this basis there should be allowed for the healthy child of average activity about 12 gm. carbohydrate per kilogram at 1 year, decreasing to between 9 and 10 gm. or about 1 per cent. of the body weight, at 6 years and maintaining about this value throughout the remainder of the growth period.

If the total caloric need is raised above the average by increased muscular activity, carbohydrate may be used to provide the entire amount of extra energy, since an increase in muscular activity does not increase the needs in protein or fat above the normal.

SUMMARY

1. Carbohydrate is a desirable and probably an essential component of the diet, although it does not have any specific function in nutrition. It forms the largest part of the diet at all periods of life.

2. Nursing infants take on the average about 12 gm. carbohydrate per kilogram of body weight daily. Artificially fed infants usually receive somewhat more than this.

7. Holt, L. E., and Fales, H. L.: Am. J. Dis. Child. **22**:371 (Oct.) 1921.
8. Holt, L. E., and Fales, H. L.: Am. J. Dis. Child., to be published.

3. The carbohydrate in the diet of the infant is almost all sugar, that of the nursing infant entirely lactose, that of the artificially fed infant usually a mixture of lactose with saccharose or maltose and dextrins.

4. The carbohydrate intake of more than one hundred healthy children from 1 to 18 years of age, studied by us, averaged 10 gm. per kilogram. Of this 51 per cent. was sugar, including lactose, saccharose and fructose, and 49 per cent. was starch.

5. Carbohydrate is more economical than fat or protein, both physiologically and commercially. Because of this latter advantage there is a growing tendency to increase the proportion of carbohydrate in the diet beyond the amount which is desirable.

6. When a very large proportion of the food is in the form of carbohydrate, the intake of fat or of protein or of both is likely to be less than the normal nutritive need of the body.

7. A diet excessive in carbohydrate leads to an abnormal deposition of fat without a corresponding increase in muscle development. Children taking such a diet have feeble resistance to infection.

8. There is evidence that a relationship exists between the high proportion of carbohydrate in the modern diet and the prevalence of dental caries.

9. Definite digestive disturbances, chiefly intestinal, may be produced when the carbohydrate in the diet is excessive. There may result increased fermentation with loose acid stools or constipation with flatulence and abdominal distention. When long continued these disturbances are very difficult to control.

10. Carbohydrate furnishes the calories needed in the diet which are not supplied by the requisite amounts of fat and protein.

11. It seems rational to allow in the diet of the child of average activity about 12 gm. carbohydrate per kilogram of body weight at one year, decreasing the amount to about 10 gm. per kilogram at 6 years and maintaining it at this value throughout the remainder of the growth period.

12. An increase in the total caloric need because of increased activity may be supplied by carbohydrate alone.

FOOD REQUIREMENTS IN NEW-BORN INFANTS

A STUDY OF THE SPONTANEOUS INTAKE

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Food requirements are commonly estimated by one of two methods, by measuring the heat output or by measuring the caloric intake. Heat output, as measured by direct or indirect calorimetry, has been most useful and has given the most significant information in defining our standards of basal metabolism. Such information as we have on the total energy requirement has come, in the main, from measurements of the total food intake. In the new-born this has been determined from the amounts of breast milk taken by healthy infants. The summary of von Reuss,[1] condensed in Table 1 and plotted in Figure 1, includes most of the data in the literature covering this point.

There is, however, a serious objection to figures based on an assumed correspondence between intake and needs. The amount of breast milk obtained is governed by the supply available. That the supply during the first few days is not adequate has been proved by metabolic measurements and by clinical observation. Thus Benedict and Talbot [2] state, on the basis of their observations, that "even under the most favorable conditions the total amount of available energy in the colostrum which the child receives from the mother's breast during the first few days is wholly insufficient to supply the energy needs, even when we consider only the basal metabolism. Still less does this scant fuel supply serve for the probable increment above basal metabolism caused by the restlessness, crying and varied muscular activity of the infant throughout the day. It is thus seen that the struggle for existence and struggle for food begin simultaneously with the new-born infant. Since the food supply is so obviously insufficient, we may ask why nature does not provide more liberally during the first few days. It is a most striking fact that only human mothers and new-born infants are so entirely dependent on the care of others. The relationship between this fact and the development of civilization is most interesting and leads one to ask if this scant food supply is a natural consequence of civilization." The not infrequent occurrence of inanition fever dur-

* Received for publication, June 15, 1921.

* From the Division of Pediatrics, Stanford University Medical School.

1. Von Reuss, A. R.: Die Krankheiten des Neugeborenen, J. Springer, Berlin, 1914, pp. 91, 92.

2. Benedict, F. G., and Talbot, F. B.: The Physiology of the New-Born Infant, Carnegie Institution of Washington, Pub. No. 233, Washington, D. C., 1915, pp. 124-126.

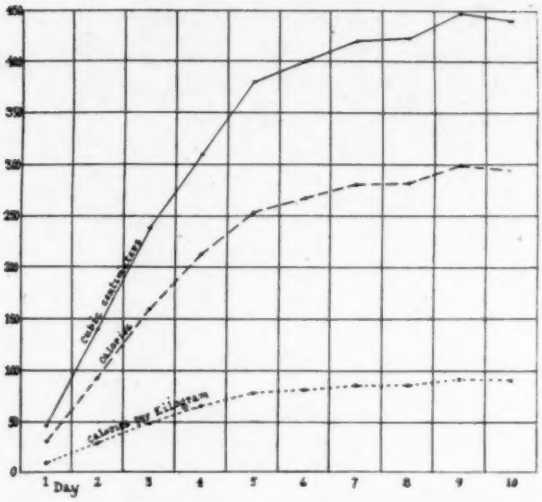

Fig. 1.—Average normal intake of breast milk. Calculated from von Reuss' compilation.

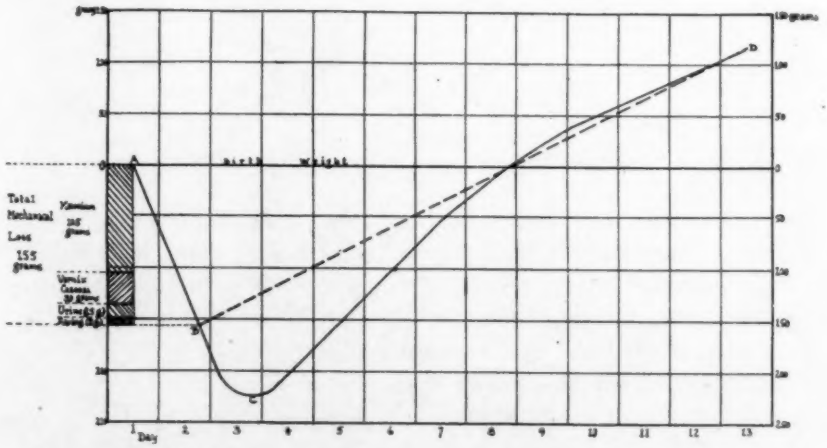

Fig. 2.—Line ACD: actual weight curve—average of 112 infants. Line ABD: theoretical ideal weight curve.

ing the first few days is direct evidence that the water supply, at least, is inadequate and it can be readily shown (Fig. 2) that the initial loss even of the most favored group of so-called normal babies far exceeds the mechanical loss. The respiratory quotient shows that during the first days the metabolic processes rapidly exhaust the stored carbohydrate and soon attack the stored fat and sometimes perhaps the body protein. Acidosis at this time is not uncommon.[2]

If we wish to know something more about the total needs for food during these first days of life we can adopt another procedure; we may offer the infant all the food which he desires and determine the amounts which he actually takes in the presence of plenty. So far as I can find

TABLE 1.—SUMMARY OF CASES SHOWING BREAST MILK INTAKE FOR FIRST TEN DAYS OF LIFE*

Day	Number Cases	Average C.c. Breast Milk	Average Calories	Average Energy Quotient	Average Weight. Gm.
1	109	46	31	9	3,250
2	155	140	93	29	
3	157	238	159	49	
4	175	319	213	66	
5	177	380	253	78	
6	179	401	267	82	
7	170	421	281	87	
8	161	423	282	87	
9	147	448	299	92	
10	64	442	295	91	
Seven Cases (Feer)					
1	...	4	3	1	3,528
2	...	50	33	10	
3	...	177	118	37	
4	...	315	210	67	
5	...	456	304	96	
6	...	549	366	116	
7	...	552	368	117	
8	...	567	378	120	
9	...	562	375	119	
10	...	603	402	127	

* From von Reuss' compilation. The original sources were in some instances consulted.

no one, except Murlin and Bailey,[3] has attempted feeding of this sort in the new-born, and their results are not reported in detail.

For reasons, into which it is not necessary to go fully, about ninety new-born infants in the wards of Lane Hospital were fed in this way. The infants were put to the breast every four hours, an effort being made to obtain for them all the breast milk available, and then given as much of one of the formulas to be described as they wished to take. By weighing before and after nursing and by measuring the quantities taken from the bottle, the total intake was determined. In all, about eighty-five records were complete enough for statistical analysis, making a total of 932 patient days or 5,592 feedings. By using the

3. Bailey, H. C., and Murlin, J. R.: The Energy Requirement of the New-Born, Am. J. Obst. **71**:526, 1915.

average figures of Holt, Courtney and Fales [4] for colostrum milk, of Van Slyke [5] for cow's milk, and of an analysis of Red Label Karo Syrup made for me by Dr. F. J. Cajori of Stanford University, the caloric values of the ingested food were determined. The variability in composition, especially of colostrum is fully recognized. This would not seriously invalidate the averages for the whole group and would only emphasize the importance of individual variation, of which a special point will be made.

During the first twenty-four hours all infants were offered 15 per cent. Karo solution with a caloric value of about 620 calories per liter. Thereafter they were offered after nursing one of the formulas shown in Table 2. These formulas were based on Pirquet's conception of

TABLE 2.—GENERAL FORMULA

Certified milk	400 C.c.
Karo corn syrup (red label)	120 C.c.
1 per cent. barley water	480 C.c.

Mix and bring to a boil.

Formula 1: with whole milk
Formula 2: with skimmed milk, taking the top 4 ounces from the quart
Formula 3: with skimmed milk, taking the top 7 ounces from the quart

	Composition			
	Fat	Carbohydrate	Protein	Cal. per Liter
Formula 2	0.6	14.0	1.3	679
Formula 3	0.3	14.0	1.3	653
Colostrum*	2.8	7.6	2.3	667
Cow's milk†	3.9	5.1	3.2	698

	Composition of Karo (Red Label)		
	Per 100 Grams		Per 100 C.c.
Water	22.98 Gm.		32.1 Gm.
Ash	1.36		1.9
Soluble carbohydrates	75.37		105.0
Suerose	1.3	1.8	
Maltose	6.0	8.4	
Glucose	24.4	34.0	
Dextrins	43.8	61.0	
Specific gravity, 1.393			

* Analyses of Holt, Courtney and Fales.
† Analyses compiled by Van Slyke.

an "equivalent milk" [6]—a mixture having approximately the same caloric value as whole milk. Fear of disorders from butter fat led to the use of a low fat percentage. The use of corn syrup, introduced in pediatrics by Marriott [7]—a highly hydrolyzed starch, consisting of dextrose and its polymers—seems logical. In our experience, practically no disturbance of digestion has followed the use of the rather high carbohydrate mixtures. Having been brought to a boil at the time of preparation, these were practically sterile.

4. Holt, L. E.; Courtney, A. M., and Fales, H. L.: A Chemical Study of Woman's Milk, Especially Its Inorganic Constituents, Am. J. Dis. Child. **10**: 229 (Sept.) 1915.

5. Van Slyke, L. L.: Modern Methods of Testing Milk and Milk Products, The Orange Judd Company, 1915, pp. 15-16.

6. Von Pirquet, C. F.: System der Ernährung, J. Springer, Berlin, 1917.

7. Marriott, W. McK.: The Artificial Feeding of Athreptic Infants, J. A. M. A. **73**:1173 (Oct. 18) 1919.

Average Intake.—Table 3 and Figure 3 show the total average fluid intake and caloric intake. The total intake rises rapidly in a smooth curve to the fifth day and then increases more slowly and somewhat irregularly to a maximum of about 600 c.c. and 400 calories on the twelfth day. Reduced to cubic centimeters and calories per kilogram, as in Figure 4 and Table 4, the intake will be seen to increase rapidly to about 150 c.c. and 100 calories on the fifth day, after which it rises more slowly and irregularly to about 160 c.c. and 115 calories on the

TABLE 3.—TOTAL INTAKE

Day	No. Cases	Average Weight, Gm.	Average Gain or Loss, Gm.	Average Total Fluids, C.c.	Average Total Calories
1	87	3,350	.....	104	69
2	86	3,226	—124	217	145
3	86	3,204	— 22	315	210
4	85	3,225	+ 21	409	272
5	85	3,268	+ 37	453	301
6	87	3,298	+ 30	483	322
7	84	3,338	+ 40	515	343
8	84	3,370	+ 32	518	345
9	84	3,392	+ 22	508	338
10	82	3,413	+ 21	525	350
11	69	3,431	+ 18	556	270
12	13	3,463	+ 32	586	390

TABLE 4.—AVERAGE INTAKE IN CUBIC CENTIMETERS AND CALORIES PER KILOGRAM

Day	No. Cases	Average C.c. per Kilo	Average Calories per Kilo
1	87	34.4	22.5
2	86	68.1	48.1
3	86	98.6	68.8
4	85	124.9	89.6
5	85	137.9	98.9
6	87	144.4	104.1
7	84	152.7	107.9
8	84	150.7	108.2
9	84	147.6*	104.2
10	82	154.5	111.0
11	69	157.2	114.6
12	13	167.3	117.3
5–12	588	149.3	105.3

* The slightly lower intake here is probably due to the fact that a number of infants were circumcised at this time.

twelfth day. In Figure 5 the relation of the caloric intake to previously established standards is shown. On the second day, the intake equals the basal needs, as determined by Benedict and Talbot; on the third day, it slightly exceeds the total average requirement of these investigators; on the fifth day, it equals the average total requirement of Heubner,[8] above which it rises slightly during the succeeding days. It should be noted here that the estimates of Benedict and Talbot do not

8. Heubner, O., and Heubner, W.: Zur Lehre von der energetischen Bestimmung des Nährungsbedarfes beim Säugling, Jahrb. f. Kinderh. **72**:121, 1910.

include an allowance for growth. The quantities of breast milk in the present series cannot be regarded as normal. There is definite reason for believing that the breast milk supply of the mothers in our wards has for several years been diminishing steadily (Fig. 6), and, in fact, this was the real reason for undertaking the present experiment. It

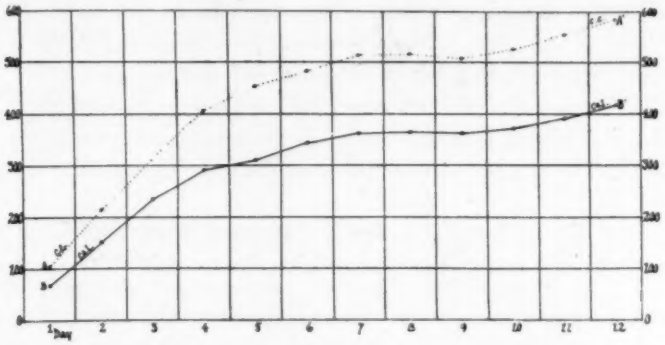

Fig. 3.—Line A-A′: average daily intake in cubic centimeters. Line B-B′: average daily intake in calories.

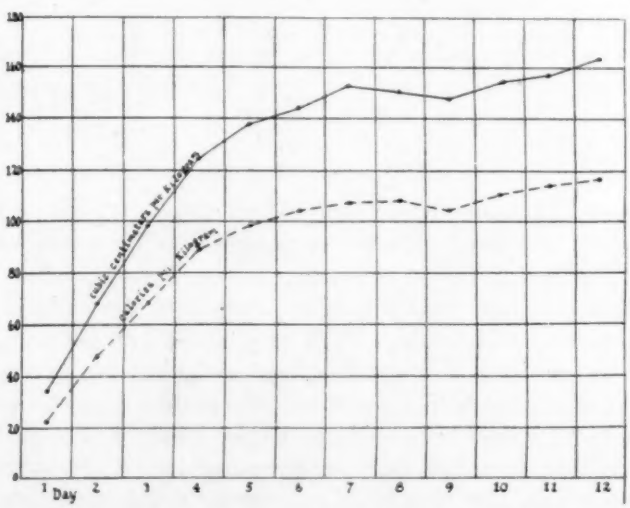

Fig. 4.—Total intake in cubic centimeters and calories per kilogram.

is of interest to note that the breast milk supply did not until the sixth day touch the level of basal requirements and had not by the twelfth day attained the level of total average requirements minus the growth quota.

Figure 7 and Table 5 show the relation of the spontaneous intake in the present series to the average breast milk supply in von Reuss'

compilation and to Feer's [9] series of seven cases in which the milk supply was especially abundant and the infants made particularly rapid progress in weight. It will be seen that for the entire breast milk series, the caloric intake is 10 or 15 calories per kilogram lower, but that in Feer's series after the fifth day the breast milk intake was 5 or 10 calories greater than in the present series. It is noted in most of the cases in von Reuss' compilation that the infants had failed to regain birth weight at the time of last observation. Figure 7 shows clearly that during the first four days, in so-called normal cases, the breast milk intake is less than the average total requirement, and even in the case of babies whose mothers have an unusually abundant supply of breast milk, the supply does not measure up to appetite until the sixth day.

Rate of Gain.—Figure 2 attempts to show what may be regarded as the ideal weight curve, compared with the actual curve of the most

TABLE 5.—ENERGY QUOTIENT OF PRESENT SERIES COMPARED WITH THAT OF FEER'S SEVEN CASES AND VON REUSS' COMPILATION

Day	Present Series	Feer's Series	von Reuss' Compilation
1	23	1	9
2	48	10	29
3	69	37	49
4	90	67	64
5	99	96	78
6	104	116	82
7	108	117	87
8	108	120	87
9	104	119	94
10	111	127	91

favored group of babies to be found in our earlier records. (The two curves were constructed before the present feeding experiment was begun.) The initial loss in the actual curve was approximately 225 gm., while the average mechanical loss (taken, in the main, from the figures of Griffith and Gittings [10]) is only about 155 gm. Regarding the latter as the ideal average loss, and assigning the average daily gain found in normal babies for the first month, a hypothetical curve is obtained which may be considered as the ideal for the first twelve days. It will be seen that supposedly normal babies with the natural breast milk supply lose about 225 gm. during the first two days, then and up to the eighth day they gain at a very rapid pace; at this time they reach the ideal level and thereafter gain at the usual rate. Figure 6 shows the average rate of gain of three unselected series of babies from three earlier periods in our wards as compared with the ideal curve, and, to the right, the incidence of inanition fever in the same

9. From von Reuss, loc. cit.

10. Griffith, J. P. C., and Gittings, J. C.: The Weight of Breast-Fed Infants During the First Two Weeks of Life, Arch. Pediat. **24**:321, 1907.

series. Figure 8 shows the composite average of the three earlier periods as compared with the ideal and with the present series. It will be seen that the curve of the present series and of the ideal are practically identical. At the right is shown the incidence of inanition fever for all the series. Actually, one case developed in the present series; this, in a baby who refused all food and who recovered only

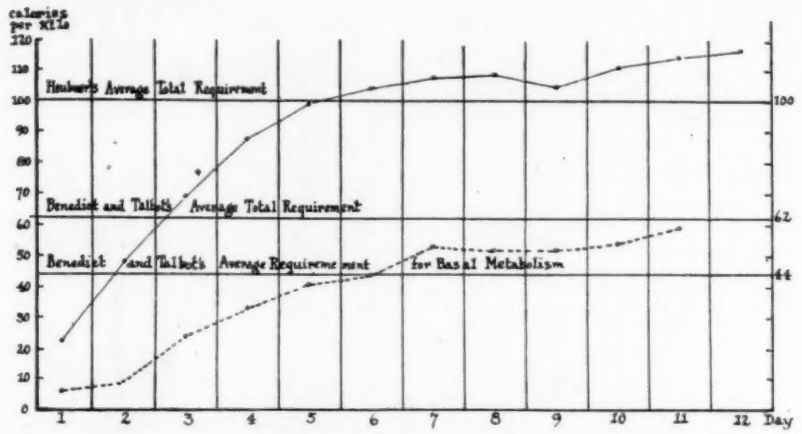
calories per Kilo
Hauber's Average Total Requirement
Benedict and Talbot's Average Total Requirement
Benedict and Talbot's Average Requirement for Basal Metabolism
100
62
44
1 2 3 4 5 6 7 8 9 10 11 12 Day

Fig. 5.—Spontaneous intake of food by new-born infants in calories per kilogram. Average of entire group. Solid line: total intake; broken line: breast milk.

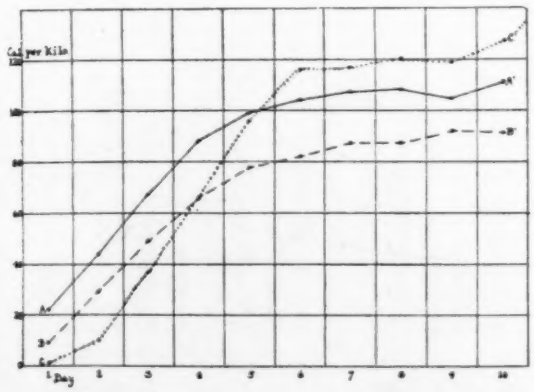

Fig. 6.—Average weight curves of three earlier periods contrasted with ideal curve.

when fed by gavage. From this figure, it appears that the average intake as determined by appetite closely corresponds with the average amount required to sustain an ideal curve of weight.

Figure 9 shows the average daily total gain plotted against the average daily total intake, from the time of low weight following the initial loss to the time of dismissal, or, as a rule, from the third to

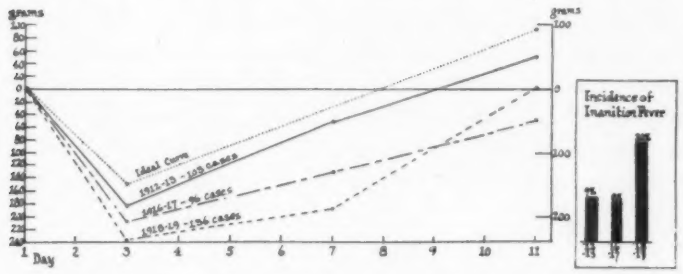

Fig. 7.—Spontaneous intake in calories per kilogram. Solid line: present series (A-A′); broken line: average nursing infant (B-B′); dotted line: Feer's seven cases (C-C′).

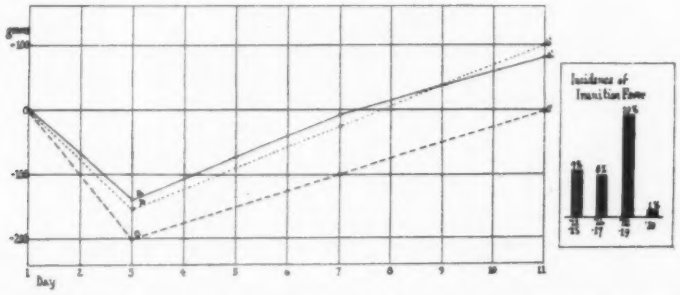

Fig. 8.—Weight curve of present series contrasted with earlier series and with ideal curve. Line a-a′: present series; line b-b′: theoretical ideal; line c-c′: average of three earlier series.

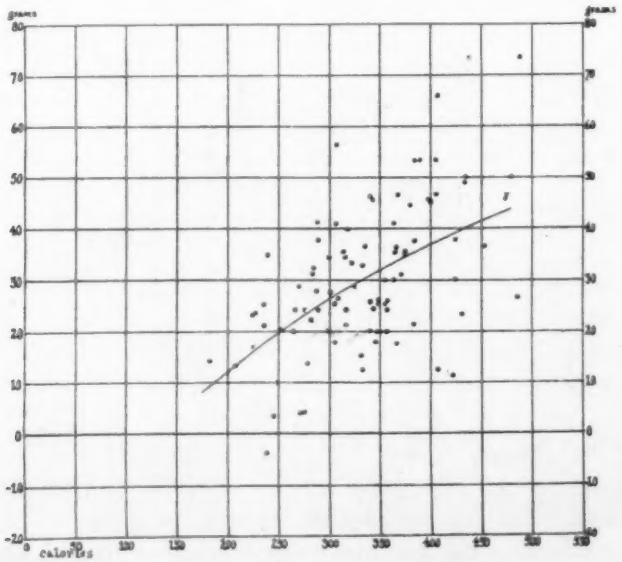

Fig. 9.—Average daily gain referred to average daily caloric intake.

the eleventh day. It shows that a satisfactory gain cannot be assured on less than 300 calories daily, and that in general, the average rate of gain follows the total caloric intake. Very striking, however, is the variability; the scatter of the graph is very wide; the proportion of calories retained for growth varies prodigiously in different infants. Figure 10 reduces the same data to calories per kilogram and gain to

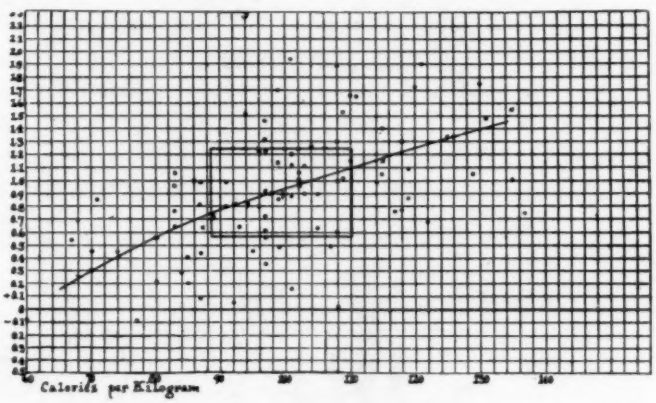

Fig. 10.—Average daily gain or loss in percentage of body weight referred to average daily caloric intake; period from third day to time of dismissal.

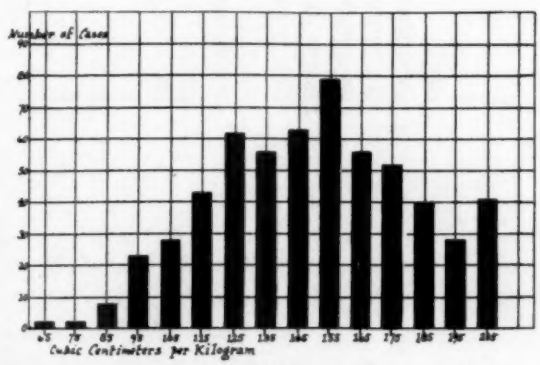

Fig. 11.—Distribution of Fluid Intakes in cubic centimeters per kilogram. Period from fifth to twelfth day inclusive.

percentages of the body weight. The variability here also is striking. It will be noted that the average daily gain is 0.9 per cent. of the body weight daily, or 9 gm. per kilogram and the intake almost exactly 100 calories per kilogram daily. The greatest concentration of measures lies between 0.57 and 1.24 per cent. of the body weight daily for gain, and between 88.5 and 110 calories per kilogram per day for intake.

Variability.—Averages at best show general tendencies; they have little bearing on the individual case unless something is known of the variability from the average of the individual components of the group. To measure variability certain mathematical methods, based on the frequency distribution, have been much used of late in the study of clinical statistics. For the purposes of the present study two frequency graphs (Figs. 11 and 12) have been made, showing the distribution of fluid intake and of energy quotient for the period from the fifth day—at which time the intake first reaches a plateau—to the time of last observation on the eleventh and twelfth days. A few infants are found who take as little as 65 and 75 c.c. per kilogram daily; for each increment of 10 c.c. the frequency increases until at 155 c.c. daily per kilogram we find the greatest number of cases. This point is the mode, or point of maximum frequency of the curve and corresponds approxi-

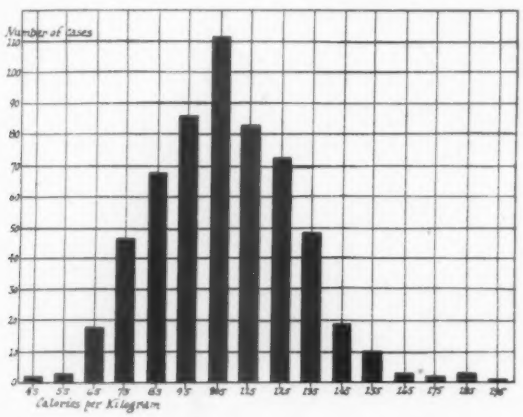

Fig. 12.—Distribution of Caloric Intakes in Calories per kilogram. Period from fifth to twelfth day inclusive.

mately with the average. With further increments of quantity, the number of cases, or frequency, diminishes, but even at 205 c.c. per kilogram we find a considerable number of cases. It is obvious that while the largest number of infants take 15.5 per cent. of their body weight daily during the period between the fifth and twelfth day, the extreme range of variation lies between 6.5 per cent. and 20.5 per cent. of the bodyweight. Likewise, in the case of calories per kilogram, while the greatest number of infants for the period took 105 calories per kilogram the range was between 45 and 195 calories. This is the extreme range. In order to separate the certainly normal from the possibly abnormal, I have suggested in another paper [11] that the stand-

11. Faber, H. K., and James, C. A.: The Range and Distribution of Blood Pressures in Normal Children and the Clinical Application of Statistical Methods to the Interpretation of Deviations from the Normal Average. (To be published in the Am. J. Dis. Child.)

ard deviation [6] of Pearson be used. Measuring off the standard deviation above and below the mean or average we find the range of certainly normal, which will include about two-thirds of the cases in most clinical statistics. We may still further restrict our range to the central 50 per cent. of cases by the use of the so-called probable error. This has certain convenient practical implications. For the period from the

TABLE 6.—Variability in Intake

Day	No. Cases	Calories per Kilogram			C.c. per Kilogram		
		Average Intake, Calories	Average Variation, Calories*	Average Variation, %	Average Intake, C.c.	Average Variation, C.c	Average Variation, %
1	87	22.5	9.2	40.9	34.4	14.7	42.7
2	86	68.8	14.4	29.9	68.1	19.6	28.8
3	86	68.8	13.1	19.0	98.6	19.5	19.8
4	85	89.6	16.3	18.2	124.9	22.9	18.3
5	85	98.9	15.7	15.9	137.9	22.4	16.2
6	87	104.1	16.7	16.0	144.4	22.6	15.7
7	84	107.9	16.4	15.2	152.7	20.5	13.4
8	84	108.2	16.2	15.0	150.7	21.6	14.3
9	84	104.2	13.7	13.1	147.6	19.0	12.9
10	82	111.0	15.0	13.5	154.5	20.0	12.9
11	69	114.6	15.7	13.7	157.2	19.0	12.1
12	13	117.3	9.6	8.2	167.3	15.1	9.0
5-12	588	105.3	15.9	15.1	149.3	21.3	14.3

* More strictly, the "probable error," which marks the limits above and below the average within which half the cases will occur. The other half will vary more than this amount from the average.

TABLE 7.—Comparison of Quantity of Breast Milk Obtained by Infants in Two Series

Day	Number of Cases		Average C.c. Breast Milk		Average Calories		Average Calories per Kilo		Average Gain or Loss		Average Birth Weight	
	First Series	Second Series	First Series	Second Series	First Series	Second Series	First Series	Second Series	First Series	Second Series	First Series	Second Series
1	4	3	31	20	21	13	6	4	....	....	3,350	3,312
2	83	60	43	43	29	29	9	9	—124	—115		
3	85	63	115	123	77	82	24	26	—22	—47		
4	83	65	183	191	122	128	38	44	+21	+21		
5	83	58	228	260	152	174	46	55	+37	+15		
6	84	58	237	277	158	185	48	58	+30	+30		
7	82	58	265	309	177	206	53	64	+40	+ 9		
8	82	56	263	315	175	210	52	65	+32	+ 8		
9	82	57	263	335	175	223	52	69	+22	— 5		
10	79	60	277	346	185	231	64	72	+21	+10		
11	65	54	300	334	200	223	58	69	+18	+16		

First series: Infants with unlimited complementary feeding.
Second series: Infants given complementary feeding only when breast milk was less than 100 c.c. per kilogram, or 67 calories per kilogram.

fifth to the twelfth day inclusive, the probable error—the variation in either direction from the mean—is 15.9 calories per kilogram and 21.3 c.c. per kilogram. The variation is, therefore, ± 15.1 per cent. for calories and ± 14.3 per cent. for fluid intake per kilogram. The range of variation of the 50 per cent. of cases nearest the average is shown for each day in Figures 13 and 14. As an example of the degree of variation it will be noted, that on the tenth day, while the average intake

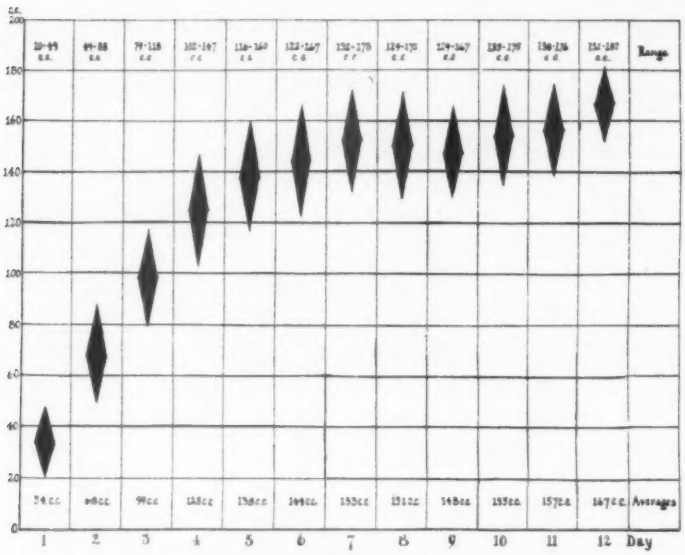

Fig. 13.—Daily fluid intake in cubic centimeters per kilogram body weight showing range of variation of 50 per cent. of the cases.

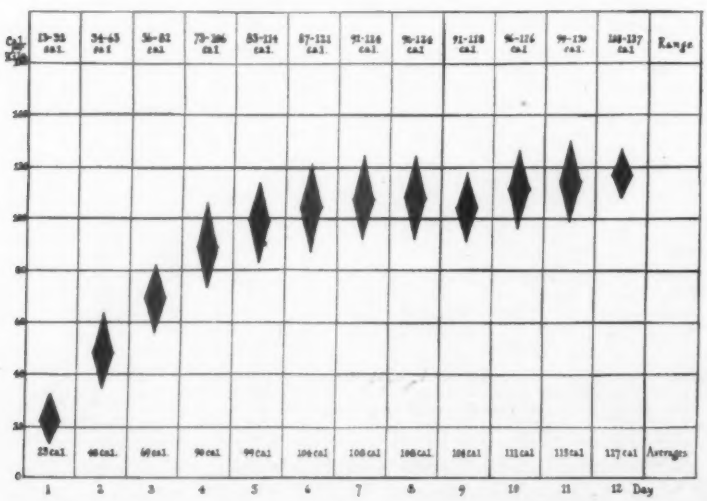

Fig. 14.—Daily intake in calories per kilogram body weight showing range of variation of 50 per cent. of the cases (± P.E.).

amounts to 111 calories per kilogram, the range of the central half of the cases extends from 96 to 126 calories. The complete figures are given in Table 6.

Since Benedict and Talbot estimate that the average total requirement of new-born infants is about 62 calories per kilogram, and since in the series here reported the spontaneous intake rose to this point on the third day and to 115 calories on the eleventh day, the question arose whether these infants were not actually taking more than they needed. Unlimited feeding was accordingly dropped, except for the first twenty-four hours; and a plan initiated by which each infant was assured at

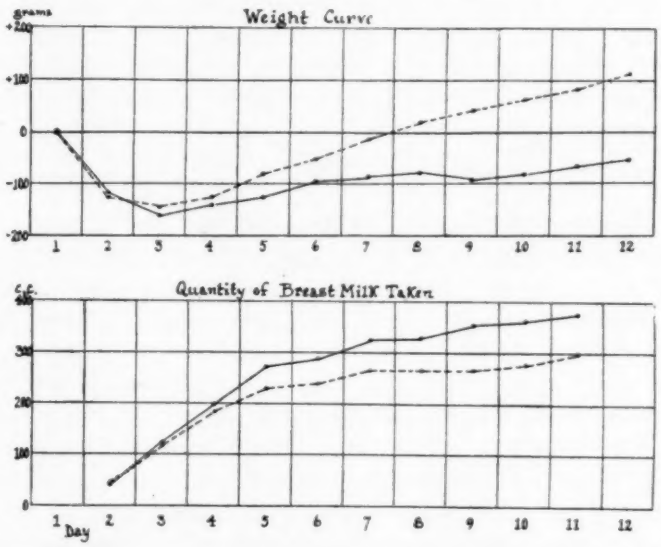

Fig. 15.—Solid line: average of babies on breast milk alone or with limited complementary feeding. Broken line: average of babies with unlimited complementary feeding.

least 100 c.c. of breast milk or equivalent formula per kilogram daily. No infant taking this amount or more of breast milk was given complementary feeding. He was thus assured about 67 calories per kilogram and any excess over this was supplied by breast milk alone. The records of sixty-two babies so fed are complete enough for analysis. The data are presented in Figure 15 and in Table 7. It will be seen that these infants obtained a little more breast milk but that the weight curve was unsatisfactory after the initial loss. That the latter was the same as for the first series was probably due to the fact that 15 per cent. Karo solution was used in the same way during the first day in both series.

COMMENT

This paper does not deal with the question of whether or not a low or inadequate intake of food during the early days of life is a useful natural provision for increasing the vigor of sucking and hence for increasing the supply of breast milk. Nor does it advocate the method of feeding employed. Its only present purpose is to show the intake of food, as energy, when the appetite of the infant is the only controlling factor, and to relate the values found with weight and rate of gain, and with the values previously determined by other methods.

As a result of the metabolic measurements of Benedict and Talbot there is at present a sharp divergence of opinion as to the caloric requirements of new-born infants. The discrepancy is more apparent than real. The measurements by these investigators show a basal rate of about 44 calories per kilogram and an estimated average total metabolism, exclusive of growth, of about 62 calories. To this figure about 15 calories [12] may properly be added as the average quota of calories retained for growth, making a total of about 77 calories per kilogram per day.

On the other hand, Heubner's figure of 100 calories as the average optimum intake has obtained abundant clinical corroboration. Beck (quoted by Morse and Talbot [14]), compiling the average breast milk intake from the literature, found, for instance, that from 1 to 12 weeks the average intake is 107 calories per kilogram. The intake figures for the first week are, as a rule, lower, and a few cases of apparently normal progress have been reported on 50 calories or less (averaged for the week). As above stated, however, the extent of the initial loss commonly regarded as normal is greater than the mechanical loss, and the figures given measure supply rather than demand.

Benedict and Talbot's figures are for the first seven days and deal with babies receiving either no complementary feeding or only small amounts of very dilute formulas. Unfortunately, they did not measure the caloric intake. The average age of the 105 infants in their series is about 2 days, 16½ hours. They found that from the second to the seventh day the minimum heat production was fairly stable.

12. Pfaundler and Schlossmann: Handbuch der Kinderheilkunde, Edit. 2, F. C. W. Vogel, Leipzig **1**:183, 1910. Here will be found Camerer and Söldner's Chemical Analysis of Six New-Born Infants. The growth quota I have calculated from this analysis (fat, 12.3 per cent.; protein, 11.7 per cent.; extractives, 1.5 per cent.; estimating extractives as carbohydrate) and from the average 9 gm. found in the present series as the daily increment per kilogram body weight. The value is in fair agreement with Camerer's [13] figure of 15 per cent. and with Rubner and Heubner's [13] figure of 12.2 per cent. of the total calories as the retention for growth.

13. Quoted from Lusk, G.: The Elements of the Science of Nutrition, Ed. 3, W. B. Saunders and Company, Philadelphia and London, 1917, p. 412.

14. Morse, J. L., and Talbot, F. B.: Diseases of Nutrition and Infant Feeding, Ed. 2, The Macmillan Company, New York, 1920, p. 73.

In the present series the average total caloric intake for the period from the second to the sixth day inclusive was 82 calories per kilogram; or, to compare the data more accurately with the Benedict and Talbot figures, the average intake from the first to the seventh day inclusive, was 77.3 calories. This is in almost exact agreement with the Benedict and Talbot estimate when 15 calories are added to the latter for growth.

During the second week the correspondence with the figures of Benedict and Talbot no longer holds. The average intake from the eighth to the twelfth days inclusive in the present series was about 107 calories per kilogram, which is in exact agreement with the results of Beck's compilation.

It would naturally be erroneous to regard the average for the first week as applying to each day of that week. Calorimetry and food measurement both assign a low value to the energy requirement on the first day. During the ensuing days the basal level is higher than on the first and it is likely that a further increase occurs when the various bodily functions get into full swing. At any rate the demands of appetite rise sharply from the second to the fifth days, and thereafter continue to increase, though not so rapidly, to the twelfth day, the last of the present series. The amounts of food substances retained for growth may also increase a little, though of this we have at present no clear indication. Calculated in the manner above indicated, the average retention appears to be 15 calories per kilogram of body weight, with a variation for 50 per cent. of the cases of between 10 and 20 calories. Digestive work and excretory waste increase proportionally with the total intake. The former may tentatively be estimated at 5 per cent. and the latter (as shown by Holt) at 10 per cent. of the total calories. Both digestive work and waste are presumably smaller (perhaps by 5 or 10 calories) on maternal than on artificial feeding. The following scheme is provisionally suggested for the apportionment of the total intake, as given in Table 4, for the period from the fifth to the twelfth day:

Basal requirements (minimum heat production)	45-55 calories
Retention for growth	10-20 calories
Work of digestion	4- 6 calories
General muscular activity	20-30 calories
Waste	8-12 calories
Total (maximum caloric needs)	87-123 calories

A word may be said as to the predictability of individual caloric needs. How closely can we estimate a given infant's total needs? Reference to Table 7 shows that after the fourth day, the probable error is about 15 per cent. of the mean values. This signifies that if we prescribe the mean or average quantity of the present series, we shall for one half of our cases be within 15 per cent. of the actual needs.

Since the probable error must be multiplied by four to cover all, or nearly all cases, it appears that the average requirement may at times fall 60 per cent. over or under the actual needs. Practically, the clinician, unless he is very conservative, will adjust his prescription for healthy infants to the point where the infant is usually satisfied. The mother who is herself regulating the baby's feeding will do likewise—she will nurse the baby until he stops crying.

SUMMARY

It appears probable that appetite provides a fairly accurate index to the needs of the new-born infant. In the series of eighty-five cases here reported, and with the formulas employed it also appeared to be a safe guide in so far as the avoidance of dangers to digestion is concerned. The demands of the infant for food exceed the basal requirements on the second day, equal the average total requirements of Benedict and Talbot on the third day; rise on the fifth day to the Heubner optimum of 100 calories, and thereafter rise slowly to about 115 calories near the end of the second week. That these demands are not excessive is indicated by the weight curve which, avoiding a greater initial loss than can be accounted for by mechanical factors, shows the same rate of gain as was previously established for healthy infants in the same community.

A final warning should be given that the method of feeding herein described, adopted for a special purpose, is not advocated for general use with breast fed infants. It may well be that for the conservation and increase of mammary secretion a period of partial starvation during the first week or two is useful or even necessary.

For infants who cannot have breast milk the claim of appetite to be satisfied may with less hesitation be given a hearing.

Grateful acknowledgment is made to Miss Katherine Crellin, head nurse of the obstetrical wards of Lane Hospital, and her assistants for the painstaking care with which the many weighings and other measurements of the present study were carried out; to Miss Fannie Hadden for valuable help with the compilations, and to Dr. F. J. Cajori of the department of chemistry of Leland Stanford Junior University for the analysis of corn syrup.

DATA IN THREE THOUSAND SEVEN HUNDRED AND FORTY-TWO PIRQUET TESTS*

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AND
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From August, 1913, to January, 1919, the Pirquet test was applied in the Babies' Hospital in 3,742 cases. It is the custom at the hospital to apply the test as a routine procedure in cases of acute and chronic illness, feeding cases, malnutrition, etc. It is not, as a rule, applied to children admitted for surgical operation for harelip, cleft palate, adenoids, tonsils, hernia, pyloric stenosis, etc. During the period covered in this study 7,494 children were admitted to the hospital. The test was applied in 3,742 cases, or in 49.9 per cent. of those admitted. The test was positive in 573 cases, or 15.3 per cent. Crude tuberculin, commonly known as Koch's O. T., furnished by the New York Department of Health, was used undiluted in every instance. The test was applied on the arm or leg. Two light scratches were made approximately ¼ inch in length and 2 inches apart. Into one scratch the tuberculin was lightly rubbed with a toothpick having a flat end; the other scratch was used as a control. In doubtful cases the test was repeated. It was not usually considered negative until forty-eight hours after application.

For purpose of study and for comparison with findings of others we have tabulated our results according to age, showing per cent. of positive Pirquet reactions (Table 1).

Of the entire group of 3,742 children tested, 2,204 were males and 1,538 females, with approximately the same proportion of positive tests for each sex, the former having 15.42 per cent. positive and the latter 15.14 per cent. positive.

The relation between white and negro children was rather significant. Although the number of negro children was small, these results confirm the observations of others regarding the greater prevalence of tuberculosis in the negro race, even in infancy and early childhood. In negro children 220 tests were made. Of these 45, or 20.45 per cent., were positive. Comparing these tests with 3,522 tests made in white children of whom only 528, or 14.99 per cent., were positive, it shows the incidence of tuberculosis among the negro race to be 5.5 per cent. higher than in the white race.

* Received for publication April 3, 1922.

As our negro patients are drawn mainly from a section of the city in which the more prosperous negroes live, it is our impression that these figures are possibly lower than the average for the whole negro population of the city.

It must be remembered that these figures in no sense bear any relation to the incidence of tuberculosis in the community generally, but only to its frequency in the particular group which furnishes hospital patients. The patients on whom these studies have been made were reared in crowded city tenements, in boarding-out homes, and under

TABLE 1.—RESULTS OF PIRQUET TEST ACCORDING TO AGE

Age	No. Tests	No. Positive Reactions	Per Cent. Positive
0-3 months	687	13	1.89
3-6 months	507	40	7.89
6-9 months	463	47	10.15
9-12 months	343	47	13.70
Under 12 months	2,000	147	7.35
12-18 months	487	83	17.04
18-24 months	363	68	18.73
12-24 months	850	151	17.76
2-3 years	371	107	28.84
3 years and over	521	168	32.24

TABLE 2.—CLINICAL DATA ON FIVE HUNDRED AND SEVENTY-THREE CASES

Age	Died in Hospital	Unimproved	Improved	Cured	Total
0-3 months	7 (53.8%)	2	1	3	13
3-6 months	22 (55.0%)	11	3	4	40
6-9 months	19 (40.4%)	10	7	11	47
9-12 months	27 (57.4%)	6	3	11	47
Total under 12 months	75 (51.0%)	20	14	29	147
12-18 months	29 (34.9%)	22	10	22	83
18-24 months	22 (32.3%)	15	5	26	68
Total 2-3 years	51 (33.7%)	37	15	48	151
24-36 months	25 (23.3%)	16	10	56	107
3 years and above	10 (5.95%)	14	12	132	168
2 years and above	35 (12.7%)	30	22	188	275
Total	161 (28.0%)	96	51	265	573

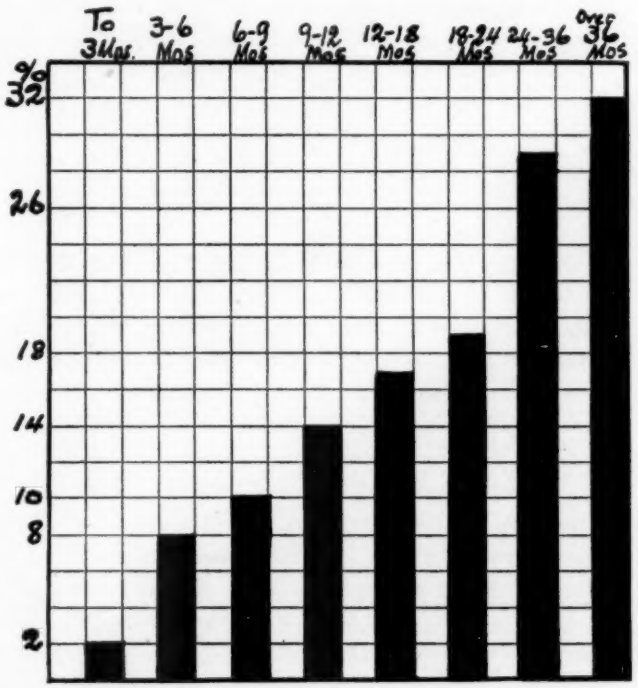
other unfavorable environments unsuited to proper growth and development. Nor in our opinion do the hospital patients of medical wards caring only for infants and very young children represent an average of the tuberculosis incidence prevailing even in what may be termed the poorer classes.

The infant usually seen in the feeding wards of such a hospital is generally one who has had a prolonged history of disturbed nutrition associated with poor hygiene and neglect. Again, there are a large number of children with tuberculous meningitis or miliary tuberculosis who have been referred to the hospital as a last resort. In the hospital

in which these studies were made there is an average admission of thirty cases of tuberculous meningitis a year. One is apt to receive the impression that tuberculous meningitis is a fairly common disease in infants; yet how infrequently are such cases, in fact any form of tuberculous infection in children, observed in private practice.

Table 2 gives the available data concerning the fate of the positive cases.

Of especial interest are 147 children under 1 year of age who gave a positive reaction. Seventy-five died in the hospital; seventeen others



Increasing prevalence of tuberculosis with advancing age, showing per cent. positive in 3,742 cases.

were removed, of whom seven had tuberculous meningitis and should be counted as fatal cases, thus making 54.6 per cent. of proven cases of tuberculosis, while ten had clinical evidence of probable tuberculosis in some other form on discharge. Twelve other children were discharged "unimproved," but without definite evidence of tuberculosis. Fourteen children were discharged "improved"; only one of these had clinical tuberculosis, while twenty-nine, or 19.3 per cent., were discharged as "cured" of the clinical condition for which they were admitted, having at no time while under observation shown any evidence of tuberculosis.

Table 3 shows the clinical evidence of tuberculosis in the ten cases removed from the hospital.

The remaining seven cases were cases of tuberculous meningitis, tubercle bacilli having been found in the spinal fluid in every instance.

Cases Between Ages of 1 and 2 Years.—Of 151 children between 1 and 2 years of age who gave a positive reaction, fifty-one died in the hospital, forty-eight were cured of the condition for which they were

TABLE 3.—DATA ON TEN CASES REMOVED FROM HOSPITAL

No.	Age, Mos.	Diagnosis	Family History and Exposure	Nursed
1	4½	Cervical adenitis	Negative	To present
2	4	Chronic tuberculosis of choroid	Ritual circumcision 8th day	To present
3	5	Acute miliary tuberculosis	Negative	To present
4	11	Pulmonary tuberculosis	Negative	3 months
5	11	Pulmonary tuberculosis	Negative	2 weeks
6	6	Tuberculous peritonitis	Negative	
7	8	Pulmonary tuberculosis	Father probably tuberculous	
8	8	Pulmonary tuberculosis	Negative	5 months
9	11	General miliary tuberculosis	Negative	2 months
10	9	Tuberculous meningitis, pulmonary tuberculosis	Negative	5 months

TABLE 4.—CLINICAL DATA ON NONMENINGITIC CASES OF TUBERCULOSIS

No.	Age, Mos.	Diagnosis	Family History	Nursed
11	17	Tuberculous peritonitis	Negative	4 months
12	24	Tuberculous cervical adenitis	Negative	
13	13	Pulmonary tuberculosis	Negative	9 months
14	19	Pulmonary tuberculosis	Negative	9 months
15	21	Pulmonary tuberculosis	Negative	20 months
16	19	Pulmonary tuberculosis	Negative	3 months
17	15	Tuberculous adenitis		
18	17	Pulmonary tuberculosis, tuberculosis of knee	Negative	Nursed to present plus artificial food at 2 mos.
19	13	Tuberculous dactylitis	Negative	11 months
20	22	Tuberculous peritonitis	Negative	5 months
21	14	Pulmonary tuberculosis	Father had tuberculous laryngitis	1 years
22	19	Pulmonary tuberculosis	Negative	10 months
23	18	Subcutaneous tuberculous abscess	Mother died of "consumption" 8 mos. ago	Never nursed
24	17	Pulmonary tuberculosis	Negative	8 months
25	11	Pulmonary tuberculosis	Negative	3 months
26	14	Tuberculous peritonitis	Negative	5 months
27	20	Pott's disease	Negative	16 months
28	17	Pulmonary tuberculosis	Negative	3 months
29	22	Pulmonary tuberculosis, tuberculous peritonitis	Mother had pulmonary tuberculosis	1 month
30	15	Tuberculous hip, tuberculous abscess	Negative	3 months
31	24	General miliary tuberculosis, pulmonary tuberculosis	Negative	1 year
32	18	General miliary tuberculosis	Negative	6 months
33	18	General miliary tuberculosis	Negative	17 months

admitted, fifteen were improved, and thirty-seven were removed against advice. Of these, twenty-nine had positive evidence of tuberculosis, six should be counted as fatal cases, as they had tuberculous meningitis when removed. This makes a total mortality of 37.7 per cent.

The clinical evidence of tuberculosis in the remaining twenty-three cases which were not meningitis is shown in Table 4.

Three of the infants discharged as "improved" had clinical evidence of tuberculosis.

One infant discharged as "cured" was in the hospital 292 days with tuberculous peritonitis.

Cases Between Ages of 2 and 3 Years.—Of 107 children between 2 and 3 years of age who gave a positive reaction, twenty-five died in the hospital, sixteen were removed, ten were discharged improved and fifty-six were cured. Of the sixteen removed, three had tuberculous meningitis and should be classed among the fatal cases, and ten had clinical evidence of tuberculosis in some other form. The total mortality, which includes the tuberculous meningitis cases, was 26.1 per cent.

Of the ten infants discharged as "improved," four had clinical evidence of tuberculosis. Of fifty-six infants discharged as "cured," two had clinical evidence of tuberculosis.

Cases at 3 Years of Age and Above.—Of 168 children three years of age and above, ten died in the hospital. Of fourteen removed against advice, eight had clinical evidence of tuberculosis of some variety. Of twelve discharged as "improved," three had evidence of tuberculosis in some form. Of the 132 discharged as "cured," none had any demonstrable signs of tuberculosis. The total mortality was 5.9 per cent.

It is a matter of importance to rule out any question of error in technic in such an analysis of cases. All the Pirquet tests in this study were made either by the resident physician of the hospital or one of the interns. These men are, in most instances, well trained and qualified to make such tests. There is always the personal equation in recording the results of the tests, which will have to be considered in any study embracing a large number of cases.

Regarding the question of the age of the tuberculin bearing on the reaction, Dr. William H. Park asserts that crude tuberculin should keep indefinitely, even at room temperature. It is possible in a large number of cases that occasionally the scarification was made either too deeply or not deeply enough, and, therefore, faulty technic might have influenced the reaction. Such an error would be discounted if the test were repeated once or successively. For this reason a second grouping is made of such cases as gave one or more negative reactions in which tuberculosis was definitely proven. There were fourteen such cases, with an average of 2.7 tests per case. As an index of the condition of the forty-four children at the time the tests were made, it should be noted that in twenty-eight instances the tests were made from one to five days before the death of the patient, and in five cases the test was done from five to eight days before death.

The fact that tuberculous infants in a very feeble condition frequently have a negative Pirquet test has been noted by many clinicians.

The poor condition of thirty-three of the patients in this group, judging their condition by the number of days intervening between their admission and death, probably explains the negative tests. However, nine infants had sufficient resistance to live ten days or more, and in these

TABLE 5.—Negative Pirquet Reactions in Forty-Four Cases of Tuberculosis, Proved by Necropsy or the Finding of Tubercle Bacilli in the Sputum or Spinal Fluid

No.	Age, Mos.	Diagnosis	Days in Hospital	No. Tests	Positive Findings of Tuberculosis at Necropsy in Spinal Fluid and Sputum
34	15	Miliary tuberculosis	4	1	Necropsy
35	6	Miliary tuberculosis	5	1	Bacilli in sputum
36	42	Miliary tuberculosis	15	1	Necropsy
37	7	Miliary tuberculosis	1	1	Necropsy
38	14	Miliary tuberculosis	6	1	Necropsy
39	19	Miliary tuberculosis	3	2	Necropsy
40	9	Tuberculous meningitis	3	2	Necropsy
41	9	Miliary tuberculosis	9	3	Necropsy
42	22	Tuberculous meningitis, Pott's disease	10	2	Bacilli in spinal fluid
43	9	Miliary tuberculosis	3	2	Necropsy
44	8	Miliary tuberculosis	7	1	Necropsy
45	15	Tuberculous meningitis	7	3	Necropsy
46	12	Tuberculous meningitis	5	4	Bacilli in spinal fluid
47	11	Miliary tuberculosis	3	1	Necropsy
48	19	Tuberculous meningitis	5	2	Necropsy
49	1½	Tuberculous enteritis, miliary tuberculosis	2	1	Necropsy
50	30	Miliary tuberculosis, tuberculous peritonitis	42	2	Necropsy
51	43	Tuberculous meningitis	3	1	Bacilli in spinal fluid
52	11	Miliary tuberculosis, pulmonary tuberculosis	34	1	Bacilli in sputum
53	8	Miliary tuberculosis	24	2	Necropsy
54	9	Tuberculous meningitis	1	1	Bacilli in spinal fluid
55	29	Tuberculous meningitis	12	7	Bacilli in spinal fluid
56	14	Tuberculous meningitis	1	1	Necropsy
57	40	Tuberculous meningitis	3	2	Necropsy
58	11	Miliary tuberculosis	5	1	Necropsy
59	13	Tuberculous meningitis	3	1	Necropsy
60	7	Miliary tuberculosis	5	1	Necropsy
61	3	Miliary tuberculosis	4	1	Necropsy
62	10	Miliary tuberculosis	3	1	Necropsy
63	3½	Tuberculous meningitis	3	1	Necropsy
64	19	Tuberculous meningitis	10	1	Necropsy
65	42	Tuberculous meningitis	16	3	Necropsy
66	2	Marasmus	30	1	Necropsy
67	20	Empyema-pericarditis	2	1	Necropsy
68	11	Tuberculous meningitis	3	2	Necropsy
69	18	Tuberculous meningitis	2	1	Necropsy
70	36	Acute purulent pericarditis	8	1	Necropsy
71	5	Miliary tuberculosis	1	1	Necropsy
72	8	Tuberculous meningitis	6	1	Necropsy
73	4½	Regulation of feeding	3	1	Necropsy
74	30	Tuberculous meningitis	4	1	Necropsy
75	16	Tuberculous meningitis	5	1	Necropsy
76	13	Tuberculous meningitis	3	1	Necropsy
77	18	von Jaksch's anemia	..	1	Necropsy

we should expect the test to be positive. Of these nine infants four had miliary tuberculosis, and in two the test had been repeated. Four were cases of tuberculous meningitis. The test had been repeated in three, and in one case it had been repeated six times. One of the nine infants had marasmus, and although it lived thirty days, it is

probable that the poor nutrition of the infant was the cause of the negative reaction.

The following cases included in Table 5 seem of sufficient interest to merit further comment:

SYNOPSIS OF CASES

CASES 1 AND 2 (Nos. 46 and 65).—Japanese, ages 12 months and 3½ years, respectively; tuberculous meningitis. The first child was admitted in poor condition and had four negative tests while under observation. The second child was admitted in good condition and had three negative tests while under observation.

CASE 3 (No. 60).—Age, 7 months. Discharged from the hospital eight days previously with a diagnosis of ileocolitis, "cured." At the same time the Pirquet test was positive. When readmitted, the child's condition was poor and the Pirquet test was negative. The father was in the hospital under treatment for pulmonary tuberculosis.

CASE 4 (No. 49).—Age, 6 weeks, breast feeding exclusively, abdomen distended since birth, no known exposure to tuberculosis.

Of this group of forty-four cases with negative Pirquet tests and positive evidences of tuberculosis, seven infants had been entirely breast fed from birth.

Of the entire group of forty-four cases of proven tuberculosis with negative Pirquet tests, twenty infants had tuberculous meningitis; nineteen others had miliary tuberculosis (seventeen proved by necropsy and two by finding tubercle bacilli in the sputum). The other five infants had other forms of tuberculous infection demonstrated at necropsy. Of those with tubeculous meningitis, fifteen had poor or very poor nutrition, four had fair, and only one had good nutrition. Of those with miliary tuberculosis, twelve had poor or very poor nutrition and seven had fair nutrition.

The youngest of these infants was 6½ weeks old, and the oldest 43 months. Twenty-two of the children were under 12 months.

0- 3 months	4 cases
3- 6 months	3 cases
6- 9 months	9 cases
9-12 months	6 cases
12-18 months	8 cases
18-24 months	5 cases
24-36 months	4 cases
36 months and over	4 cases

Positive Reactions in Breast-Fed Infants Without History of Exposure.—Thirty-one cases have been assembled with the view of presenting the difficulty of determining the mode of infection of many of the cases of tuberculosis in infancy and childhood.

It has often been stated that the most dangerous types of persons with pulmonary tuberculosis are those who do not known they have the disease and those who think they have been cured. In obtaining

a history of exposure, the first type cannot be excluded, except by the most rigid social service cooperation, which has not been at any time available to us. In so far as the so-called "cured" cases are concerned, we believe that a careful history generally elicits the information that some one in the family has had pulmonary tuberculosis at some time. In twenty-nine of the thirty-one cases, the children had been nursed entirely up to the time of admission to the hospital, or within a few days to a week prior to admission. In two of the cases the infants had been nursed twelve and fourteen months, respectively; the former was 14 months of age and the latter 18 months.

The fact that twenty-nine of the infants had been nursed entirely would seem to rule out the possibility of a bovine infection. Nineteen of the thirty-one infants had either tuberculous meningitis or miliary tuberculosis or both, one had tuberculous cervical adenitis, and one

TABLE 6.—CASES WITH POSITIVE OR DOUBTFUL REACTION AND NEGATIVE NECROPSY FINDINGS FOR TUBERCULOSIS *

No.	Age, Mos.	Diagnosis	Family History and Exposure	Findings at Necropsy	Pirquet Test
78	13	Empyema.....	Negative	Bronchopneumonia; no tuberculosis	Positive
79	9	Acute bronchopneumonia.	Negative	Negative for tuberculosis	Doubtful, probably negative
80	17	Marasmus; tetany.....	Negative	Glioma of brain; negative for tuberculosis	Four slightly positive tests, negative after 24 hrs.
81	10	Glioma of cerebellum.....	Negative	Tumor of cerebellum; negative for tuberculosis	Doubtful, counted negative
82	26	Cerebral tumor; chronic hydrocephalus	Negative	Glioma of brain; negative for tuberculosis	Slightly positive
83	15	Pneumococcus septicemia; tetany; empyema	Negative	Negative for tuberculosis	Slightly positive

* It is of interest, but probably of no significance, that in three of these cases a brain tumor was found at necropsy.

had pulmonary tuberculosis with tubercle bacilli in the sputum; none of the others had a demonstrable tuberculous lesion, yet all had a positive reaction. In view of the fact that every infant in this group of cases had been breast-fed, it seems probable that in every instance the infection was acquired from a human contact. In spite of this presumption, certainly in thirty of the thirty-one cases, the history offered no evidence that the parent or parents were aware of the fact that the child had been in contact with a tuberculous person. The average age for the thirty-one infants was 8 months.

Positive Reactions in Very Young Infants.—The details relating to thirteen infants under 3 months of age with positive reactions are especially important because the mother had positive tuberculosis in four instances and there was a probable tuberculous exposure in three instances. In six cases there was no history of tuberculosis in the

family and no exposure was known. Of the four cases in which the mother definitely had tuberculosis three of the infants had proven tuberculosis, and the fourth infant was discharged "cured" of the condition for which it was admitted. In the three cases with a probable

TABLE 7.—Positive Reactions in Breast-Fed Infants Without Exposure

No.	Age, Mos.	Diagnosis	Family History and Exposure	Nursed
84	14	Tuberculous meningitis, miliary tuberculosis..	Negative	1 year, + solid food since
85	8	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
86	4½	Tracheal stenosis due to tuberculous bronchial lymph nodes	Negative	Entirely
87	18	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
88	4	Acute cervical adenitis	Negative	Entirely
89	7½	Miliary tuberculosis, tuberculous meningitis, tuberculous enteritis	Negative	Entirely
90	12	Tuberculous meningitis, miliary tuberculosis..	Negative	11½ months, artificial feeding since
91	4	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
92	11	Tuberculous meningitis	Uncle who lived in same house 8 mos. had pulmonary tuberculosis	Entirely
93	11	Pulmonary tuberculosis	Negative	Entirely
94	5	Pulmonary tuberculosis, miliary tuberculosis..	Negative	Entirely
95	10	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
96	8	Pyelitis	Negative	Entirely
97	5	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
98	8	Tuberculous meningitis	Negative	Entirely
99	9	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
100	5	Acute miliary tuberculosis	Negative	Entirely
101	5½	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
102	3	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
103	10	Tuberculous meningitis, miliary tuberculosis..	Negative	Entirely
104	14	Ileocolitis	Negative	Entirely
105	4	No disease		Entirely
106	15	Tetany		Entirely
107	12	Acute bronchopneumonia	Negative	Entirely
108	1½	Acute gastro-enteritis		Entirely
109	5	Retropharyngeal abscess		Entirely
110	6	Tuberculous meningitis	Negative	Entirely
111	7	Secondary anemia		Entirely
112	6	Defective cerebral development		Entirely
113	7	Tuberculous meningitis		Entirely
114	9	Tuberculous meningitis		Entirely

TABLE 8.—Data Regarding Nine Children 12 Months Old or Less When Pirquet Reaction Positive

No.	Age at Test, Mos.	Age at Present, Mos.	Race	Present Weight, Pounds	Information Obtained by Field Worker
128	11	30	Negro	..	Very healthy child, well nourished
129	6	34	American	..	Neighbor states that child is healthy
130	7	12	Italian	..	Mother states child is well; field worker noted child was pale
131	12	55	German	38	Mother states he is healthy
132	10	48	American	..	Healthy
133	2	18	Italian	20	Coughs, underweight
134	12	54	Italian	35	Underweight, no symptoms
135	8	48	Hungarian	39	Healthy
136	3	32	Irish	27½	Healthy

exposure, one infant died and had tuberculous lesions at necropsy; the remaining two were discharged from the hospital; one was "improved" and the other "unimproved." Of the six infants without a history of exposure two died in the hospital. Positive findings were recorded at

necropsy. Another infant died of meningococcus meningitis. Necropsy was not obtainable. Three infants were discharged "cured."

Of the thirteen cases, there was no other evidence of tuberculosis than the skin test in six, while the patients were under observation. Six patients died of tuberculosis in the hospital. It was possible to obtain data regarding only one of the six patients discharged from the hospital. At the time this information was secured the child (No. 127) was 14 months old, weighed 11 pounds 11 ounces, and was under treatment for "spastic paralysis."

SUMMARY OF CASES

Case 5 (115).—White, aged 2 months; in hospital thirty-eight days. Nursed two weeks. Mother is in hospital with laryngeal tuberculosis. Necropsy: General miliary tuberculosis and tuberculous meningitis.

Case 6 (116).—White, aged 3 months; in hospital six days. Artificially fed. Mother has active pulmonary tuberculosis; cared for infant. Tuberculous skin lesions. Tubercle bacilli found in sputum.

Case 7 (117).—White, aged 3 months; in hospital eight days. Artificially fed. Mother living at home had pulmonary tuberculosis. Tuberculous meningitis.

Case 8 (118).—Negro, aged 3½ months; no exposure; nursed one month.

Case 9 (119).—White, aged 2½ months. Maternal grandmother has pulmonary tuberculosis. Nursed one month.

Case 10 (120).—White, aged 2 months; in hospital twenty days. Mother thought to have pulmonary tuberculosis. Nursed one day.

Case 11 (121).—White, aged 9 weeks; in hospital thirty days. Mother in hospital with pulmonary tuberculosis. Artificially fed.

Case 12 (122).—White, aged 3 months. Died after three days' observation. Family history and exposure negative. Nursed three weeks. Tubercle bacilli found in sputum. Tuberculous lesions found at necropsy.

Case 13 (123).—White, aged 3 months. Diagnosis: Tuberculous meningitis. Family history and exposure negative. Nursed entirely. Tuberculous lesions found at necropsy.

Case 14 (124).—White, aged 6 weeks; in hospital four days. Discharged "cured." No family history or exposure. Nursed entirely.

Case 15 (125).—White, aged 2½ months. Diagnosis: Meningococcus meningitis. Died. No necropsy. No family history or exposure. Two Pirquet tests, both slightly positive.

Case 16 (126).—White, aged 2 months. Diagnosis: Tuberculous meningitis. Tuberculous lesions found at necropsy. Mother probably tuberculous. Nursed three days.

Case 17 (127).—White, aged 3 months. Family history and exposure negative. Nursed one month. Now 14 months old. Weight 11 pounds 11 ounces. Diagnosis: "Spastic paralysis."

Relation to Exposure.—In a group of 433 cases, which includes children with positive and negative Pirquet tests with positive findings of tuberculosis as necropsy in spinal fluid or sputum, there was a relation to exposure in a considerable number of the cases.

Exposure definite in 77 cases, or 17.7 per cent.
Exposure very probable in 10 cases, or 2.3 per cent.
Exposure probable in 21 cases or 4.7 per cent.
No history of exposure in 325 cases, or 75 per cent.

THE VITAL CAPACITY OF THE LUNGS OF CHILDREN

A PRELIMINARY REPORT *

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It is now definitely recognized that disease of the lungs or of the heart may produce a considerable reduction in the vital capacity of the lungs. Due to the fact that the normal lung capacity, particularly for children, is not generally known, clinicians have experienced difficulty in estimating accurately the extent of the reduction in vital capacity existing in individual cases. As a result such determinations are rarely included in the routine examination of children suffering from alleged cardiac or pulmonary disease.

Rather extensive series of observations made on healthy children have been published especially by Gilbert,[1] Smedley,[2] Baldwin,[3] Emerson and Green [4] and Wilson and Edwards.[5] Unfortunately, most of these data have appeared in journals not readily accessible to the medical profession. We wish to contribute vital capacity averages for 430 healthy children (228 boys, 202 girls), ranging in age from 4 to 15 years inclusive. In addition, observations are reported for five children having bronchiectasis, and for five with tuberculosis.

The vital capacities were measured by means of an accurately calibrated wet spirometer. The children were instructed to take the deepest possible inspiration, and then to empty the lungs completely into the spirometer. Each child was given several trials, and the maximum amount repeatedly expired was recorded as the vital capacity.

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5. Wilson, M. G., and Edwards, D. J.: Vital Capacity of the Lungs and Its Relation to Exercise Tolerance in Children with Heart Disease. Standards for Normal Vital Capacity for Children. The Lung Capacity in Certain Intrathoracic Conditions, Am. J. Dis. Child. **22**:443 (Nov.) 1921.

When the cooperation of the child was unsatisfactory the observations were discarded. Care also was taken to include no child suffering either from acute respiratory infections, or from chronic heart or lung disease.

The children were weighed naked, and at the same time the standing height was recorded. The sitting height was measured with the child seated on a chair against a perpendicular scale.

The vital capacity of the lungs for the boys (Table 1) shows an increase with advancing age, from an average of 792 c.c. at 4 years to 3,044 c.c. at 15 years, a gain of 2,252 c.c. For the girls, during a

TABLE 1.—AGE, NUMBER OF NORMAL BOYS AND GIRLS, AVERAGE VITAL CAPACITY (SEXES SEPARATED)

Age, Years	Number of Boys	Vital Capacity Boys, C.c.	Vital Capacity Girls, C.c.	Number of Girls
4	6	792	644	9
5	15	936	819	12
6	19	1,161	1,055	26
7	27	1,320	1,214	18
8	32	1,480	1,337	17
9	37	1,740	1,511	19
10	14	1,828	1,740	23
11	24	1,954	1,782	19
12	16	2,309	2,061	19
13	18	2,383	2,288	24
14	15	2,653	2,525	8
15	5	3,044	2,681	8

TABLE 2.—WEIGHT, NUMBER OF NORMAL BOYS AND GIRLS AND VITAL CAPACITY (SEXES SEPARATED)

Weight, Kg.	Number of Boys	Vital Capacity Boys, C.c.	Vital Capacity Girls, C.c.	Number of Girls
10-15	3	978	693	7
20	45	1,071	975	50
25	66	1,438	1,366	39
30	38	1,786	1,675	34
35	29	2,058	1,911	33
40	24	2,323	2,081	13
45	11	2,509	2,377	11
50	6	2,800	2,533	6
55	5	3,108	2,713	4

similar period the averages increase from 644 c.c. to 2,381 c.c. Thus for the latter the growth in lung capacity amounting to 1,737 c.c. is considerably less than that accomplished by the former (2,252 c.c.). The data also show the vital capacity to be constantly lower for girls than for boys at corresponding ages.

In Tables 2, 3 and 4 the data are averaged (sexes separated) according to body weight (in kg.), standing height (in cm.) and sitting height (in cm.), respectively. At this time we will call attention merely to the fact that at either corresponding weight, standing height, or sitting height, the average vital capacity is constantly greater for the

boys than for the girls. The actual averages for the different body measurements recorded may be obtained by reference to the proper table.

In addition to presenting data for normal children, we are also able to report vital capacity records for five children having bronchiectasis (Table 5). These children were examined by one of us, while working at the Mayo Clinic. The diagnosis in each instance was confirmed by roentgen-ray examination of the lungs. The children gave histories of repeated attacks of bronchitis extending over a long period, and at

TABLE 3.—STANDING HEIGHT, NUMBER OF NORMAL BOYS AND GIRLS AND AVERAGE VITAL CAPACITY (SEXES SEPARATED)

Standing Height, Cm.	Number of Boys	Vital Capacity Boys, C.c.	Vital Capacity Girls, C.c.	Number of Girls
95–100	5	732	625	5
105	7	850	742	9
110	12	967	902	17
115	19	1,163	1,082	21
120	25	1,323	1,182	10
125	27	1,442	1,302	20
130	33	1,638	1,495	16
135	24	1,790	1,730	14
140	20	1,984	1,835	23
145	15	2,227	1,926	25
150	8	2,413	2,175	10
155	16	2,510	2,348	11
160	13	2,842	2,527	15
165	7	3,210	2,812	3

TABLE 4.—SITTING HEIGHT, NUMBER OF NORMAL BOYS AND GIRLS AND VITAL CAPACITY (SEXES SEPARATED)

Sitting Height, Cm.	Number of Boys	Vital Capacity Boys, C.c.	Vital Capacity Girls, C.c.	Number of Girls
55–57.5	13	855	812	13
60.0	18	1,074	1,020	26
62.5	23	1,250	1,149	17
65.0	39	1,408	1,367	26
67.5	37	1,624	1,589	21
70.0	37	1,909	1,823	28
72.5	19	2,127	1,881	21
75.0	17	2,347	2,075	14
77.5	15	2,533	2,406	17
80.0	7	2,900	2,557	7

the time seen complained of frequent colds, chronic cough, abundant sputum and were in general poor health. With Subjects 1 and 2 (Table 5) definite clubbing of the terminal phalanges of the fingers and toes was noted. Physical examination in each instance revealed the presence of numerous coarse râles particularly at the bases of the lungs.

The data (Table 5) show the existence of a considerable reduction in vital capacity for the first four patients, which is especially pronounced (46 per cent.) for Subject 2. Subject 4 was examined on a second occasion, and her vital capacity again registered 750 c.c.

This time she was instructed to endeavor to free the bronchi of accumulated secretion by postural cough with the head hanging downward and at a lower level than that of the chest. After expectorating a considerable amount of sputum in this manner, the vital capacity was again recorded, and was found to have increased from 750 to 1,150 c.c. For Subject 5 the vital capacity actually exceeded the normal average, expected for corresponding age. This girl, however, had been freeing the lungs of excessive secretion by means of postural cough for several weeks, which possibly was a factor in enabling her to register a vital capacity equal to the normal.

Although five cases is too small a number to justify any sweeping statements, nevertheless, it appears safe to conclude that bronchiectasis usually produces a definite reduction in the vital capacity of the lungs, which may be very marked in severe cases. In certain instances, however, the vital capacity may be practically normal in spite of the presence of definite chronic disease of the lungs. A normal vital capacity consequently does not necessarily indicate that the lungs are in a perfectly normal condition.

TABLE 5.—AGE IN YEARS, STANDING HEIGHT IN CM., WEIGHT IN KG., VITAL CAPACITY IN C.C., AND NORMAL VITAL CAPACITY FOR CORRESPONDING AGE FOR FIVE CHILDREN HAVING BRONCHIECTASIS

Case Number	Age, Years	Standing Height, Cm.	Weight, Kg.	Vital Capacity, C.c.	Normal Vital Capacity for Corresponding Age, C.c.
Boys:					
1	8	127	21.4	1,000	1,480
2	15	168	41.0	1,375	3,044
Girls:					
3	6	120	24.1	800	1,055
4	7	121	18.0	750	1,214
5	12	147	30.5	2,200	2,061

The vital capacity measurements for five children having tuberculosis are recorded in Table 6. For the two boys the vital capacity of the lungs is extremely subnormal. The first boy has an advanced and active tuberculosis of the lumbar spine complicated by a large psoas abscess. The roentgenograms of the lungs revealed diffuse mottling and fibrosis throughout both lung fields. About six months later a second determination was made, and the vital capacity showed a decrease from 1,050 to 775 c.c. The hospital records revealed that this boy had failed gradually in strength during this period, and was in a much poorer general condition than when first examined.

The second boy's vital capacity is also greatly reduced. He has a healed Pott's disease of the thoracic vertebrae, with extensive ankylosis and a marked kyphosis. Numerous scars of healed sinuses are present along the spine. The roentgen-ray revealed a chronic fibroid condition

in the lungs. In spite of the enormous reduction in vital capacity, this boy was able to undergo considerable activity with comparatively little dyspnea.

The vital capacity for the first one of the three girls reported is practically normal for her age. She had an active tuberculosis of the hip with many discharging sinuses. The roentgen-ray revealed normal lung fields, and only moderate enlargement and calcification of the glands at the root of the lungs.

The second girl has an advanced and active pulmonary tuberculosis with many areas of consolidation in each lung. Numerous räles are present on both sides, and examination of the sputum revealed many tubercle bacilli. As might be expected, the vital capacity of the lungs of this patient was greatly reduced.

TABLE 6.—AGE, STANDING HEIGHT, WEIGHT, VITAL CAPACITY, NORMAL VITAL CAPACITY FOR CORRESPONDING AGE, LOCATION AND EXTENT OF DISEASE FOR FIVE CHILDREN HAVING TUBERCULOSIS

Case Number	Age, Years	Standing Height, Cm.	Weight, Kg.	Vital Capacity, C.c.	Normal Vital Capacity for Corresponding Age C.c.	Location and Extent of Tuberculosis
Boys:						
1	13	142	21.8	1,050	2,383	Lumbar spine; psoas abscess
2	15	131	23.2	750	3,044	Thoracic spine; marked hyphosis; chronic fibroid; pulmonary tuberculosis
Girls:						
3	11	138	29.0	1,000	1,782	Hip; many sinuses; lungs negative
4	15	151	50.1	950	2,681	Advanced pulmonary tuberculosis
5	13	146	25.1	575	2,288	Advanced pulmonary with cavities

The third girl has an advanced pulmonary tuberculosis with cavities present in each lung. At the time the record was made the girl was up and about, and practically free from dyspnea on mild exertion, in spite of the fact that her vital capacity was only slightly more than one third the normal expected for corresponding age. The observation recorded was obtained about three months previous to the death of the patient.

These cases illustrate the extreme reduction in the vital capacity of the lungs which may result from pulmonary tuberculosis. Undoubtedly, these patients at one time had a normal vital capacity, but following the development of a tuberculous infection, the vital capacity apparently progressively decreased as the pathologic process advanced. Repeated determinations made during this period probably would have given striking and unmistakable evidence through the progressive diminution in vital capacity, that the pathologic condition present in the lungs was gradually increasing. While single measurements of

the vital capacity are no doubt of value in detecting the presence of pulmonary diseases, repeated determinations are vastly more valuable, for changes in the pathologic process present are promptly reflected by fluctuations in the vital capacity of the lungs. Therefore, the progress of the disease may be followed by noting the effect on the vital capacity. Instead of relying on indefinite clinical notes or memory regarding the presence of abnormal breath sounds, or extent of areas of dulness, etc., recorded on previous examinations, an accurate measurement in cubic centimeters of the vital capacity of the lungs can be established from which except for the normal increase accompanying growth there should be very little constant deviation on subsequent examinations. The occurrence of any permanent reduction in the vital capacity below previous determinations apparently will give immediate clue to the development or extension of pathologic processes within the chest.

SUMMARY

1. The averages for the vital capacity of the lungs of 430 healthy children (228 boys; 202 girls), grouped according to age, weight, standing height and sitting height, are recorded. The averages show the vital capacity of the lungs to be constantly greater for the boys than for the girls of corresponding age and size.

2. Vital capacity records are reported for five children having bronchiectosis and also for five children suffering from tuberculosis, which demonstrate the marked reduction in vital capacity which these conditions may produce.

NEUROPATHIC MANIFESTATIONS IN INFANTS AND CHILDREN AS A RESULT OF ANAPHYLACTIC REACTION TO FOODS CONTAINED IN THEIR DIETARY *

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The close association of the exudative and neuropathic diatheses suggests a causal relationship. The frequent anaphylactic nature of the former [1] would seem to point toward a similar cause in the latter. It is my purpose in this paper to discuss certain nervous manifestations in infants and children from the standpoint of anaphylactic cause.

It is hardly necessary to call attention to the frequent occurrence of the exudative and neuropathic diatheses in the same individual. All observers recognize the common association. However, it seems to have been generally held that this relationship is nothing more than accidental. Czerny considered it so.[2] He felt that the almost universal presence of the neuropathic diathesis in one or both parents of children with the exudative diathesis led, as a natural result, to the neurotic child. The degree to which the infant was affected by this nervous environment determined, to a certain extent, the obstinacy and severity of the exudative manifestations. Pfaundler [3] stated that the sneezing in coryza, pertussoid in bronchitis, asthma in bronchiolitis, severe colic in enteritis, etc., were dependent, to a certain degree, on the coexistence of a neuropathic diathesis along with the exudative diathesis.

This common association, together with the fact that frequently in the same individual the symptoms of one, and again the symptoms of the other diathesis, will seem to predominate, led me to the opinion that not infrequently the symptoms of both conditions might be due to the same underlying factor. Inquiry revealed the fact that often nervous patients have a history, either personal or familial, of exudative disturbances, and the frequent anaphylactic basis for the exudative phenomena suggested that the nervous symptoms might also be due to this cause. Therefore, this investigation was undertaken to see if this might not be the case clinically.

The cases presented are of three types; first, the type in which the symptoms of both diatheses were plainly present; second, the type in

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* From the Miller Hospital Clinic.

1. Shannon: Minnesota Med. **5**:137. (March) 1922.
2. Czerny: Monatschr. f. Kinderh. **7**:1. 1908.
3. Pfaundler: (Quoted from Leo Wolf). Jahrb. f. Kinderh., **4**:175.

which the present symptoms were nervous but in which there was a definite exudative history; and third, the type in which the symptoms were those of the neuropathic diathesis without a history of frank exudative phenomena preceding. With one case experimentation was possible.

REPORT OF CASES

CASE 1. A girl, 5 years of age, presented an uriticarial eruption and asthma. The mother stated that the patient was very high-strung and nervous. There was a history of hay-fever in the father and of eczema in several cousins. Skin tests revealed positive erythematous reactions to several foods of which the patient was eating a great deal. Removal of the offending foods from the patient's diet resulted in early relief from nervous manifestations and from the uriticaria and asthma.

CASE 2. A boy, 2 years and 8 months of age, had a history of a very itchy skin eruption, apparently of an urticarial nature, rather loose stools, and extreme nervousness. Whereas he normally slept well at night and took a nap during the daytime, of late he would not sleep at all during the day and very poorly at night. He was very irritable.

Cutaneous tests showed erythematous reactions to a number of foods he was eating. Modification of the diet and eliminating as much as possible the foods to which he was sensitive resulted in complete disappearance of the skin and nervous symptoms in two weeks' time. The child became himself again, was not irritable, slept well at night, and took a long nap during the daytime.

CASE 3. A boy, 4 years old, had a history of eczema and asthma. He was extremely high-strung and very nervous. His appetite was rather poor and he was very finicky about what he ate. He slept poorly at night. The mother complained that he could not sit still and that he was very hard to manage. Skin tests revealed erythematous reactions to a large number of foods and to a number of animal emanations. The diet was regulated and he was instructed to stay away from the animals to whose proteins he was sensitive. Relief from asthmatic symptoms had occurred nine days later and the eczema had improved considerably. Eighteen days after the tests were performed he was still free from asthma and there was only a slight chapping of the cheeks. The nervousness had improved greatly. His general restlessness was gone. He slept better at night and slept well during the daytime. His appetite was very good and he had gained 2½ pounds in weight. At the present time, one month after the institution of treatment, the improvement has continued.

CASE 4. A girl, 28 months old, was brought in because of an urticarial eruption and nervousness. Local treatment for the urticaria only was advised. Three weeks later she was brought back. The skin condition seemed improved, but the mother stated that the child was very irritable. She was unruly, peevish, ate poorly, and did not sleep well.

Skin tests revealed positive reactions to a number of foods the patient was eating in rather large quantity. These included egg and wheat. A diet was advised eliminating, as nearly as possible, the offending foods. Improvement was noted one week later but the mother said that she had been giving store cookies containing both egg and wheat to the patient. These were discontinued and after another interval of two weeks there was considerable improvement, especially in the nervousness. The mother asserted that the child "could be reasoned with." On one occasion the patient had been given spaghetti and tomatoes for her evening meal and both skin and nervous symptoms were much worse thereafter. At the present time, six weeks after the tests were performed, the nervousness is gone and the skin is clear.

CASE 5. A boy, 12 years of age, had been subject to eczema when an infant, to hives as he grew older, and still later to attacks of asthma. All these symptoms had been absent for a number of years, with the exception that he had

had an attack of urticaria a few months previous to the first observation. The present complaint was that of fever for the past few days, extreme nervousness, constant stuffiness in the nose, occasional attacks of vomiting, and frequent headaches. He was extremely introspective, cried easily, was very irritable, and was constantly "out of sorts."

A period of hospital study revealed a chronic inflammatory condition of the nasal sinuses. Treatment of this condition resulted in relief from the headaches and disappearance of the fever and nasal obstruction. However, the nervousness remained.

Skin tests revealed sensitization to several foods, a number of pollens, although the parents had never suspected the presence of hay-fever, and to horse dandruff and dog hair. A diet was advised and the patient instructed to stay away from dogs and horses.

Prompt improvement in the nervous symptoms resulted and this has been permanent over a period of seven months, except for a single attack of vomiting.

CASE 6. A boy, 8 years old, was brought in because he was extremely irritable, did not eat well, was cruel to his playmates, and was unable to apply himself at school. As a result of the latter condition, he spent two years in the first grade.

He had been perfectly normal, except that he had had head colds almost from birth until he was 4 years old. At that time he had had a series of convulsions without ascribable cause. He was studied by nerve specialists, internists, and eye, ear, nose and throat men, the final impression of the physician in charge being that the convulsions were due to a "food poisoning" of some kind. There had been no convulsions since that time.

A complete physical examination, including blood, spinal fluid and urine studies, Wassermann test, Pirquet test, failed to reveal anything abnormal. There was no family history of sensitization phenomena. Cutaneous tests revealed positive erythematous reactions to wheat, spinach, egg white, whole egg, pear, orange, pea, beef and figs. Questionable reactions were obtained to lactalbumin and banana. The patient was instructed to eat no wheat cereal or pastries, spinach, egg white, pea, orange, pear, beef, figs, or banana. He was to eat rye bread.

Nothing was heard from him for six weeks, when the mother reported that the boy had been a different child from the time he had gone on the diet. His irritability was lessened; he was no longer cruel to his playmates; he was doing well in school, and his appetite was good. When heard from again three months after the diet was instituted the improvement had continued and he had made his grade in school without difficulty.

CASE 7. A boy, 9 years of age, suffered from extreme nervousness and attacks of vomiting. The periodic attacks ordinarily came on infrequently, not oftener than once a month. Usually he would vomit but once but was always indisposed for several days thereafter. Between the attacks he was irritable, slept poorly, and was very finicky about what he ate. He was extremely high-strung. For the past two weeks he had been vomiting every third day, would eat almost nothing between attacks, and was so irritable that he was a problem to his parents.

His past history was negative for protein sensitization, with the possible exception that he had been a difficult feeding case from 3 to 14 months of age. From that time until four or five years he had been perfectly well. The vomiting attacks began at that time. He always coughed when he caught cold. When first seen he had been under treatment for some time for nasal sinusitis.

The immediate family history was negative for asthma, hay-fever, urticaria, or eczema. One sister had had similar vomiting attacks at one time in her life. One cousin could not eat eggs because they poisoned her. The paternal grandfather had had attacks of difficult breathing in his old age which apparently resembled asthmatic attacks.

Physical examination revealed nothing except that the patient was somewhat pale and undernourished. He was, therefore, tested with the foods of his dietary. Positive erythematous reactions were obtained to wheat leucosin, wheat gliadin, wheat proteose, pea, pineapple, potato and navy bean. The reactions to fig, brazil nut and rye were questionable.

The patient was instructed to eat no peas, navy beans, string beans, lima beans, pineapple, figs or brazil nuts. He was to eat potato no more than four times weekly, and no wheat cereal or pastries made from wheat flour. Rye bread only was to be eaten, with the exception of a small amount of white bread toast. Arrowroot or corn-starch were to be used for thickening gravies.

Improvement was almost immediate. There were no more vomiting spells. His appetite became ravenous. The mother said that she could not "fill him up." All signs of nervous irritability ceased very shortly after the diet was instituted. He began to sleep all night and to waken refreshed, which he did not do before. During the following month his class standing rose from thirteenth, where it had been constantly for five months past, to eighth, without any conscious effort on his part. At present, two and a half months after the diet was prescribed, there has been no return of either nervousness or vomiting.

CASE 8. Girl, aged 5 months, suffered from undernutrition.

The family history was unfortunate. The child was illegitimate and nothing was known of the father. The mother was committed to an institution for the feebleminded after deserting the infant.

The baby was partially breast fed for two months and since that time had been fed on milk mixtures. Cream of wheat was added to the infant's diet and seven days thereafter it was noticed that the child was extremely restless. There was constant movement of the arms and legs, with jerky movements of the entire body. The infant constantly turned and twisted in her crib. She cried incessantly day and night and slept but little throughout the twenty-four hours.

No cause was found on physical examination. There was no evidence of infection; the skin was clear and the stools normal. The symptoms were attributed to a nervous diathesis, dependent on the questionable heritage, and bromids were prescribed. These afforded marked relief and were discontinued after a short time. The infant immediately reverted to her former condition. Again bromids were given and the condition was controlled for a considerable period. However, they gradually lost their effect and about three months later (January, 1922), the patient's condition was as bad as it had been before the bromids were started.

January 25 cutaneous tests were performed with several cereals, vegetables and cow's milk. Positive reactions were obtained to wheat leucosin, proteose and globulin. All of the rest were negative. Wheat cereal was discontinued and oatmeal substituted. The bromid was discontinued.

One week later the child's disposition had changed remarkably so that it was noticed by all who came in contact with her. She slept all night and was playful and happy during the daytime. She cried but little. She had gained 7½ ounces during a period of four days.

February 5 cream of wheat was again added instead of the oatmeal. Twelve hours later a return of the old irritability was noticeable. She was very restless all the next day, turning, twisting, and throwing herself about in her crib. That night she slept less well and cried a part of the night. The symptoms continued throughout the seventh and that night she cried all night. February 8 the cream of wheat was discontinued and oatmeal again substituted. Improvement was prompt and by the night of the thirteenth the patient slept all night. By February 17 she was happy and playful, as she was during the first experimental period. Since that time she has remained so.

Of the cases cited the first four presented skin eruptions. The natural explanation for the nervousness in these cases is that it is the

reasonable accompaniment of the skin irritation. However, in all but Case 1 the nervous manifestations were out of all proportion to the severity of the skin lesions. Nevertheless, the nervous disturbances cleared up under specific therapy directed at the cutaneous, and, in some cases, the respiratory symptoms. Furthermore, in Case 4 the skin lesions were better at the time of the second visit than they were when the patient was first seen, whereas the nervousness was much worse.

Case 5 presented no skin eruption to account for the nervousness. True, there was a chronic focus of infection in the nasal sinuses which might, in a measure, have accounted for at least a part of it. However, under treatment this focus cleared up without improvement of the nervous symptoms, and it was not until the unexpected, wide-spread sensitization was found and treatment directed against this factor was instituted that improvement in his neuropathic tendencies occurred. Whether the nervous symptoms were due mainly to food, pollen or animal sensitization is purely conjectural and immaterial since we should expect that they might be the result of all these anaphylactic causes.

Cases 6 and 7 were purely nervous cases. While an anaphylactic basis for Case 7 was suggested by the history of periodic attacks of vomiting,[4] such attacks are also described as being one of the manifestations of the neuropathic diathesis. The results obtained in each case were so definite as to leave no doubt that the symptoms complained of were due to anaphylactic reactions to foods contained in the diets of the patients. In Case 8 it was possible to relieve or bring on the nervous symptoms by removing from or adding to the patient's diet the food to which she was sensitive.

That anaphylaxis might be responsible for nervousness in man through irritation of the nervous system is sound theory. Anaphylaxis is fundamentally a nervous phenomenon. Besredka emphasized this fact and founded his method for the production of shock on this principle.[5] The symptoms as seen in the experimental animal support his contention. The extreme irritability and restlessness noted immediately on injection, the scratching of the muzzle, frequently the sneezing, the dyspnea due to bronchiolar spasm, later the sudden hopping movements, and finally the convulsion itself are undisputable evidence that the nervous system is profoundly affected.

In man nervous manifestations are inseparably associated with anaphylactic phenomena. The extreme nervousness noted in individuals accompanying attacks of asthma, hay-fever, urticaria and eczema are common knowledge. Often these attacks have been attributed to

4. Schloss: Am. J. Dis. Child. **19**:433 (June) 1920.
5. Besredka: Anaphylaxis and Antianaphylaxis (English Translation). 1919, C. V. Mosby Co., St. Louis, p. 13.

nervousness, the patient not recognizing the fact that, perhaps, both the nervousness and the attack are ascribable to the same cause.

The effects of drugs on anaphylactic phenomena are further support for the nervous origin of the symptoms. Epinephrin, so valuable in asthma and urticaria, atropin and even morphin are notable drugs that act on the nervous system. Even general anesthetics greatly modify the character of an anaphylactic shock.

There is, then, an abnormal condition occurring very commonly in infants and children which would seem to give rise fundamentally to irritative phenomena of the nervous system. Is it not reasonable that such a phenomenon might give rise to all manner of symptoms ascribable to nervous origin within the body? Might it not be responsible for any of the symptoms frequently placed under the caption of the neuropathic diathesis? In fact, is there any limit within the field of the so-called functional nervous diseases beyond which such a cause could not be operative?

SUMMARY

Eight cases showing marked evidences of the presence of the so-called neuropathic diathesis in infants and children have been presented. In four of these definite evidence of the exudative diathesis was also present, while in still another there was a positive history of such a condition in the past. The remaining three cases gave no evidence suggestive of the presence of an exudative diathesis. All the patients showed the presence of protein sensitization by cutaneous tests. All showed definite relief from the nervous symptoms on the institution of specific therapy directed at the proteins to which they were sensitive. In all but one of the eight cases the proteins concerned were those of foods contained in the dietaries of the patients. In one case animal emanations or pollen proteins might have played a part. In one case the nervous symptoms could be relieved or brought on by the exclusion from or the addition to the diet of the food to which the patient was sensitive. Evidence is presented showing that anaphylaxis is a sound, theoretic basis for the explanation of many of the symptoms of the so-called neuropathic diathesis.

CONCLUSIONS

1. Many of the symptoms of the neuropathic diathesis in infants and children are not infrequently the result of irritation of the nervous system resulting from anaphylactic reactions to food proteins to which the patient has become sensitized. It is recognized that any protein to which the patient is sensitive might also be causative.

2. The frequent association of the exudative and neuropathic diatheses in infancy and childhood is, therefore, something more than accidental, the presence of each frequently being attributable to the same cause.